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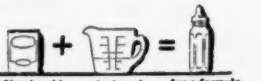

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THE A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN is published by the American Medical Association as a medium for the advancement of knowledge of the diseases of children and for the publication of scientific investigation in this field.

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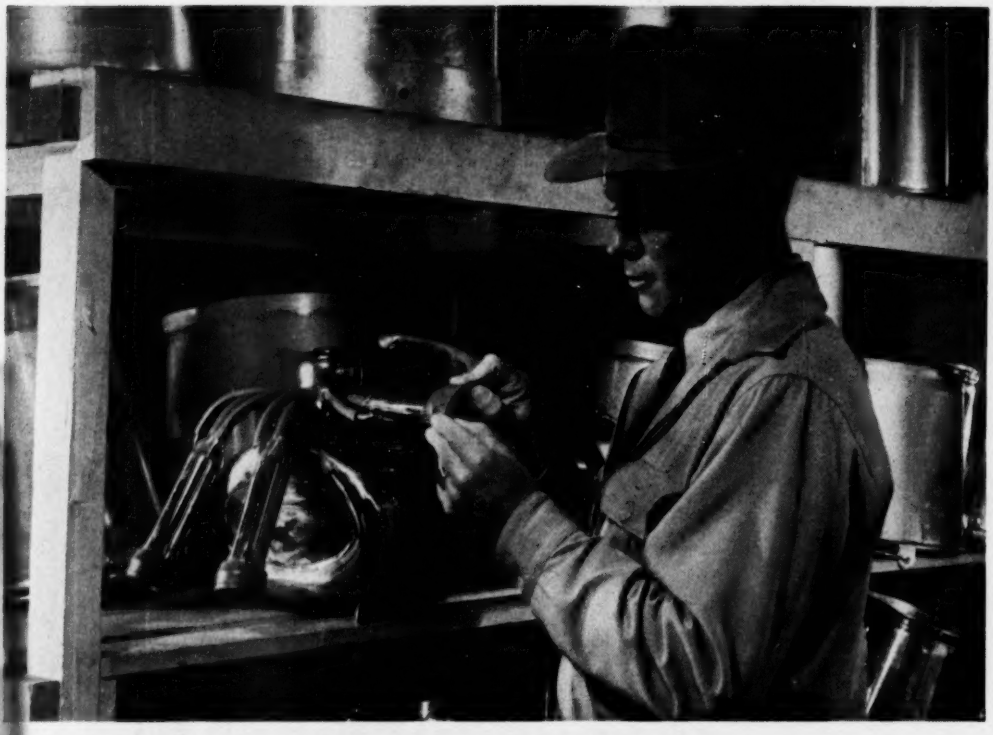

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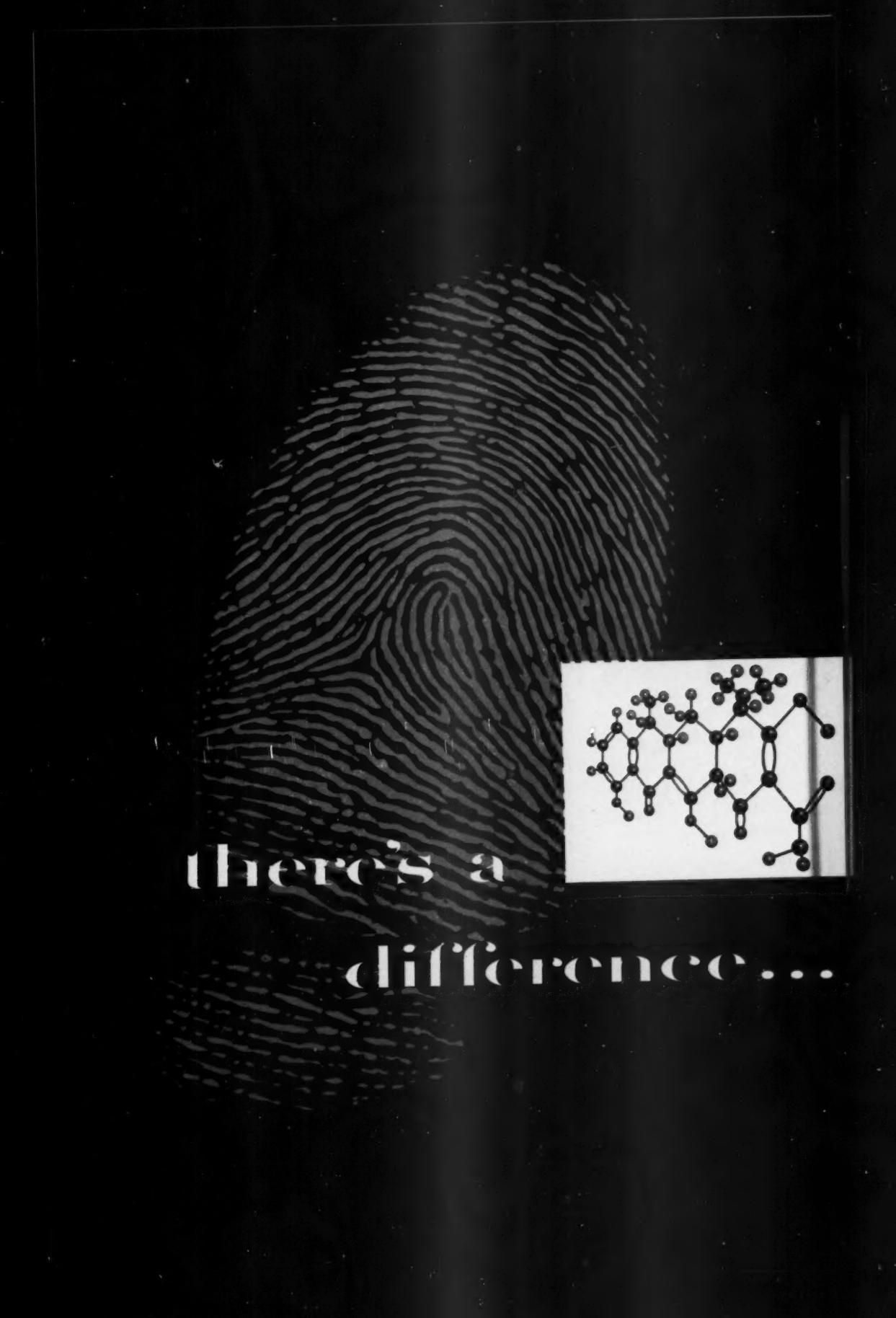
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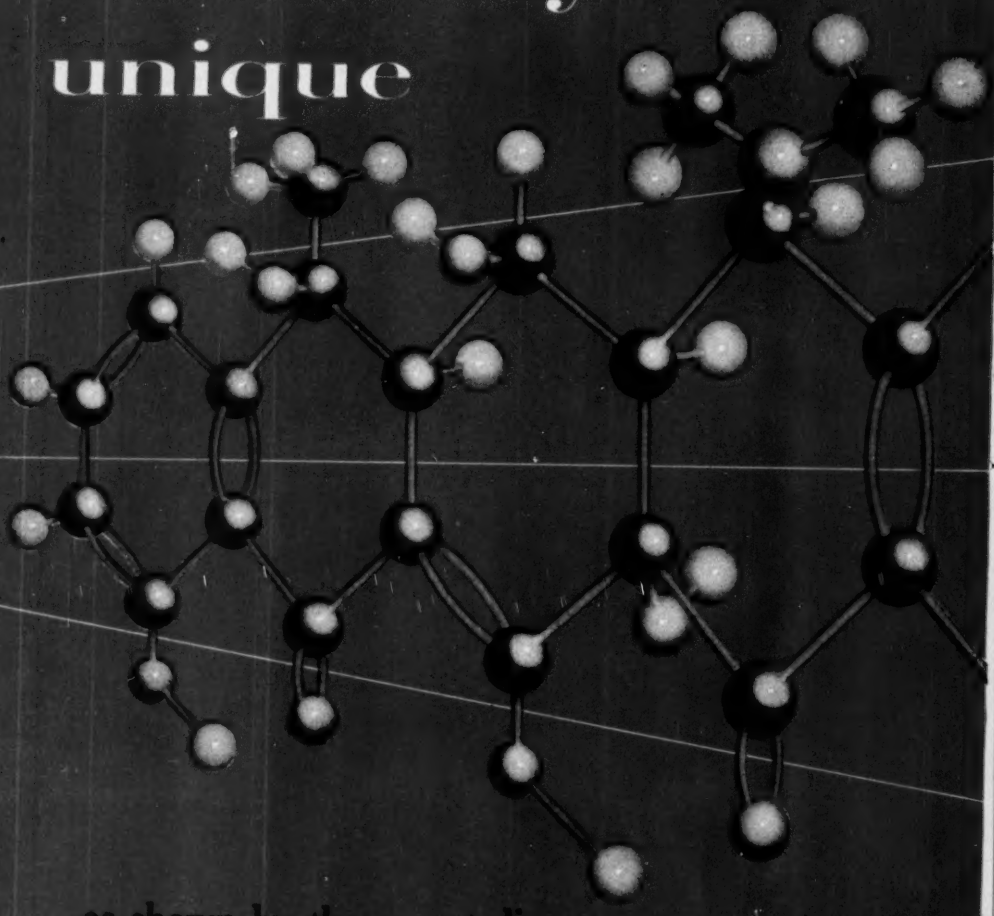

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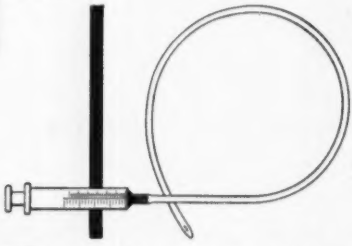

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	7	3.8		
	1154	4.0	0.7	
	7	3.8	2.3	8.0
	27	4		6.8
	45	3.2	3	
	408	3.4	1.0	5
	184	4.8		6.2
	5	3.8	1.3	
	94	3.3		8.3
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1. Muller-Stephans, H.: Ztschr. Kinderheilk. 67:495, 1950.
2. Salmi, T.: Acta Paediatrica: 22:1, 1948.

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*Journal of Pediatrics *39: 325 1951*
**Bull, Johns Hopkins Hosp. *87: 569 1950*

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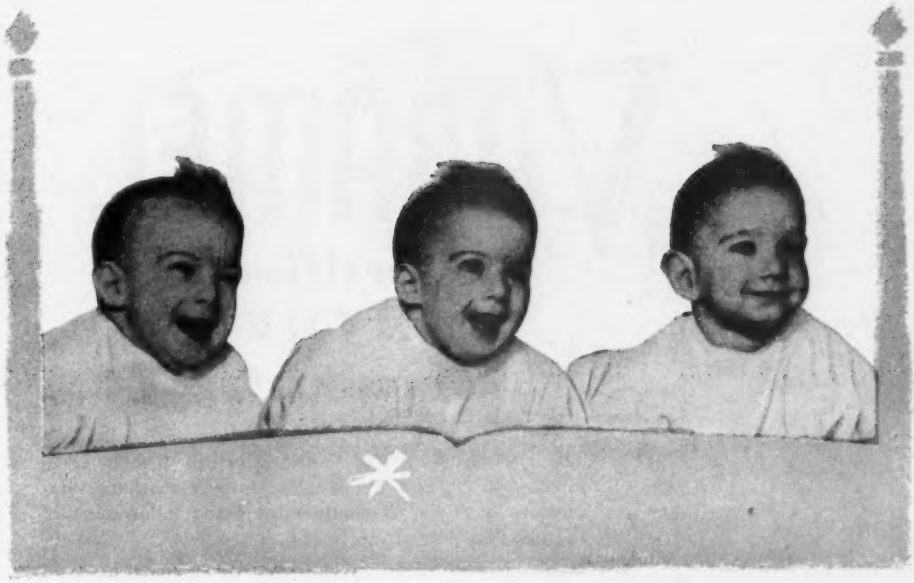

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*Sobel, S. H.: Milk Allergy in a case of Triplets, *Clin. Med.*, August 1952.

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American Journal of Diseases of Children

VOLUME 84 OCTOBER 1952 NUMBER 4

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TREATMENT OF CONVULSIONS IN CHILDHOOD

M. G. PETERMAN, M.D.
MILWAUKEE

A CONVULSION is the most serious symptom which can occur in childhood. It demands an immediate investigation as to its cause or origin. A complete and detailed description of the convulsion from the beginning to the end is the most useful aid in the attempt at localization and cause. The classification of convulsions introduced in 1934 [1] and subsequently revised, in 1946,[2] has been a very useful working chart to indicate the most probable cause of the convulsion. An accurate family history, particularly of convulsive seizures, is invaluable in this study. While an electroencephalogram [3] is not essential in most cases when the history is adequate, it is the greatest diagnostic aid in medicine.[4] With this sensitive apparatus it is possible to discover a potential convulsive state before a seizure has occurred.[5] It is also possible to evaluate the results of treatment and to determine the need for continuation of treatment. The electrogram has been of particular value in determining the importance of the febrile convulsions in childhood.[6] It has also helped to discover and confirm the diagnosis of one of the most serious manifestations of epilepsy in which there may have been no seizure, namely, psychomotor epilepsy or psychic equivalent.[7] This apparatus has clarified the organic basis of akinetic seizures, or "nodding spasms," in young children.[8]

The introduction of the many new drugs in the past 10 years, and especially of drugs with marked specificity in the treatment of the various types of epilepsy, has made it particularly important to establish and confirm the diagnosis of the convulsive disorder and to determine, if possible, the exact type.[9] The best known and the least expensive of all the anticonvulsants, phenobarbital, is almost a specific in adequate dosage for the control of major, or grand mal, epilepsy. It has absolutely no value in the treatment of petit mal, or minor, epilepsy, or of most of the

This study was supported in part by grants from Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y., and Abbott Laboratories, North Chicago, Ill.

1. Peterman, M. G.: J. A. M. A. **102**:1729 (May 26) 1934.
2. Peterman, M. G.: Am. J. Dis. Child. **72**:399 (Oct.) 1946.
3. Peterman, M. G.: Wis. Med. J. **43**:708 (July) 1944.
4. Peterman, M. G.: J. A. M. A. **138**:1012 (Dec. 4) 1948.
5. Peterman, M. G.: South. Med. J. **41**:62 (Jan.) 1948.
6. Peterman, M. G.: J. A. M. A. **143**:728 (June 24) 1950. The latest report is to be published in J. Pediat.
7. Gibbs, F. A.: J. Pediat. **15**:749 (Dec.) 1949.
8. Penfield, W., and Kristiansen, K.: Epileptic Seizure Patterns: A Study of the Localizing Value of Initial Phenomena in Focal Cortical Seizures, Springfield, Ill., Charles C Thomas, Publisher, 1951.
9. Peterman, M. G.: J. Kansas M. Soc. **41**:277 (July) 1940.

other forms.[10] On the other hand, trimethadione (tridione®),[11] the first drug we have ever found to be effective in the treatment of petit mal epilepsy, will control one third of the cases of this disorder but may precipitate a grand mal seizure or status epilepticus in the person with this potential type of convulsive disorder.[12]

It is most unfortunate that there are some physicians who create false hopes and unwarranted optimism in the minds of the ever-hopeful epileptic patients and their families. True enough, investigators are working on a multitude of compounds in the hope of finding more effective anticonvulsant agents; however, it must be realized that no drug has yet even equaled phenobarbital as an anticonvulsant for children. Those who have had no familiarity or experience with diet treatment dismiss or deprecate the ketogenic diet, and yet fasting and purging remain the most effective treatment of epilepsy that we have ever had. The ketogenic diet is based on an attempt to reproduce the results of fasting in the control of seizures and still supply adequate nutrition. Like the diabetic diet, it is not a fancy menu, nor is it automatic in operation. One fact stands out: In the largest series of private epileptic patients treated for the longest period, the ketogenic diet has been the most effective treatment available and the one with no harmful side effects.[13] Livingston

TABLE 1.—*Immediate Treatment of Convulsions in Childhood*

1.	Phenobarbital sodium subcutaneously, intramuscularly, or intravenously every 6 hours until desired effect is produced
2.	Magnesium sulfate by mouth or by rectum in 50% solution, intramuscularly in 25 to 50% solution, or intravenously, slowly, in 20 to 25% solution
3.	Paraldehyde by mouth, by rectum, intramuscularly, or intravenously
4.	Chloral hydrate by mouth or by rectum
5.	Chloroform or vinyl ether by inhalation
6.	Oxygen, when convulsion prolonged
7.	Tribromethanol (avertin®) by rectum
8.	Spinal fluid drainage and air replacement
9.	Thiopental (pentothal®) sodium, continuous intravenous drip

has reported the following results with the ketogenic diet: complete control in one third of the cases, marked improvement in one-fifth, improvement in one-sixth, and no effect in one-third.[14]

The treatment of convulsions today demands, first of all, an understanding of the cause of this manifestation. It is more important to study the type of the seizure and to get information as to its onset than it is to start indiscriminate treatment. The immediate treatment of a convulsion is outlined in Table 1. Let me emphasize again, as I have for the past 30 years, that opium and its derivatives are not anticonvulsants and that they are definitely contraindicated in the treatment of any convulsion. Morphine and codeine are used more than any other drugs in the immediate treatment of convulsions, but entirely without logical basis. The opiates depress respiration, inhibit peristalsis, and mask symptoms. They are definitely contraindicated in the treatment of convulsions.

After the basic cause of the convulsion has been provisionally diagnosed on the basis of the classification of convulsions according to age or has been established,

10. Peterman, M. G.: Internat. Clin. **2**:99 (June) 1935.
11. Lennox, W. G.: J. A. M. A. **129**:1069 (Dec. 15) 1945.
12. Peterman, M. G.: Am. J. Dis. Child. **75**:734 (May) 1948.
13. Keith, H. M.: Am. J. Dis. Child. **74**:140 (Aug.) 1947.
14. Livingston, S.: To be published.

TABLE 2.—*Classification of Febrile Convulsions**

	No. of Cases
Convulsions (febrile)	129
Idiopathic epilepsy	62
Cerebral birth injury residual with convulsions	34
Encephalitis with convulsions	17
Brain hemorrhage residual with convulsions	8
Cerebral dysgenesis	5
Cerebral anoxia	2
Rheumatic fever	2
Miscellaneous	20
Total	279

* A new classification is to be published in the Journal of Pediatrics.

TABLE 3.—*Organic Causes of Convulsions*

1. Congenital or developmental cerebral anomalies
2. Antenatal, natal, or postnatal cerebral injuries, or anoxia residuals
3. Antenatal, natal, or postnatal infections or poisonings and their residuals
4. Post-traumatic brain lesions
5. Toxoplasmosis

TABLE 4.—*Treatment of Major Seizures*

1. Phenobarbital
2. "Gemonil" (5,5-dimethyl-1-methylbarbituric acid)
3. Phenacemide (phenurone®)
4. "Nuvarone" (3-methyl-5-phenylhydantoin)
5. Other hydantoins
6. Bromides

TABLE 5.—*Causes of Convulsions in Children from Three to Ten Years Old*

	%
1. Idiopathic epilepsy	49
2. Acute infections	23
3. Cerebral birth injury residual	7
4. Encephalitis, acute and chronic	5
5. Post-traumatic	3
6. Meningitis	2
7. Cerebral dysgenesis	1
8. Brain tumor	1
9. Miscellaneous	9

TABLE 6.—*Causes of Convulsions in Children from Ten to Sixteen Years Old*

	%
1. Idiopathic epilepsy	73
2. Encephalitis, acute and chronic	5
3. Congenital syphilis	4
4. Cerebral birth injury residual	3
5. Miscellaneous	15

treatment may be considered. The classification of febrile convulsions is listed in Table 2. The treatment of acute convulsions due to poisoning is, of course, the removal of the poison. Convulsions due to an acute invasion of the nervous system or to infectious diseases require specific treatment of the infection and of the convulsions. The remaining convulsions may be classified as those of organic origin as listed in Table 3, and those due to epilepsy. The presently available drugs for the treatment of convulsions of organic origin are listed as to their effectiveness and priority in Table 4.

The majority of the convulsions in older children (as listed in Tables 5 and 6) are due to epilepsy.[15]

The treatment of epilepsy today must be subdivided into the treatments of the various types. As stated above, the most effective and the safest treatment of all types of epilepsy, the treatment which will not precipitate or introduce another type, is diet control. This begins with a fasting diet for 10 days or 2 weeks, which if effective is then followed by the ketogenic diet.[16] If this diet is not practical, the particular type of epilepsy should be established before drug treatment is begun. This can best be done with the electroencephalogram if this facility is available.

The treatment of petit mal should be started with trimethadione. This drug was introduced in 1944, and it is the first drug which has ever been effective in petit mal.[17] It will control approximately one third of all cases. The drug is toxic and may depress the bone marrow; therefore, blood counts must be done two weeks after treatment is initiated and monthly thereafter for six months. If trimethadione is not effective, paramethadione (paradione®), introduced in 1947, may be tried.[18] This drug is slightly less toxic than trimethadione. If the diones are unsatisfactory or unsuccessful, phenacemide (phenurone®) may be used. This drug also is toxic to the bone marrow and sometimes to the liver. Therefore precautions must be taken with blood counts and liver tests. With phenacemide, signs and symptoms of liver damage must be watched for closely. With the diones the possibility of precipitating or initiating major grand mal seizures in the child with this potential disorder must be kept in mind. Since about half of the children with petit mal eventually develop grand mal and, therefore, have this cerebral disorder, it is always advisable to give phenobarbital with the diones. Glutamic acid, glycerin, ammonium chloride, and ammonium nitrate are among the many drugs which have been suggested and discarded because of failure of action.[19] Mandelic acid, like ammonium chloride, will produce acidosis if given in sufficient amounts, but it will not produce ketosis and, therefore, it has no effect on the seizures of petit mal. The most promising drug at the present time is a carbonic anhydrase inhibitor (2-sulfonamide), a sulfone compound which produces a temporary excretion of acetone in the urine and control of seizures even after the acetone disappears within a week or 10 days.[20]

15. Peterman, M. G.: Nerv. Child. **6**:1 (Jan.) 1947.
16. Peterman, M. G.: Illinois M. J. **84**:306 (Nov.) 1943.
17. Everett, G. M., and Richards, R. K.: J. Pharmacol. & Exper. Med. **81**:402 (Aug.) 1944.
18. Davis, J. P., and Lennox, W. G.: J. Pediat. **34**:273 (March) 1949.
19. Peterman, M. G.: Wisconsin M. J. **51**:324 (March) 1952.
20. Berliner, R., and others: Am. J. Med. **11**:274 (Sept.) 1951.

The treatment of major seizures, particularly of idiopathic epilepsy, must always begin with phenobarbital. This safe, harmless drug has been the most effective anticonvulsant we have ever had. It is almost a specific in the treatment of grand mal idiopathic epilepsy. If the convulsions do not respond to phenobarbital in an adequate dosage, one should always look for some other cause than idiopathic epilepsy. I have used this drug in children for 30 years, and, except for a few insignificant rashes or occational drowsiness, I have never seen habituation, increased tolerance, or serious toxicity. Contrary to the experience of Bradley,[20a] which I am unable to understand, it is most unusual for phenobarbital to produce an agitation or psychotic reaction. If it should, I would suspect a chronic encephalitis, in which such a reaction may occur. If phenobarbital fails to control the major seizures of epilepsy when it is given in adequate dosage and properly spaced to precede the expected or usual convulsion by two to four hours, the drug of second choice is "gemonil" (5,5-dimethyl-1-methylbarbituric acid). This drug is now available. I have treated 149 patients with this compound with the following results: Thirty-one have been kept under complete control, 35 have been fairly well controlled, 45 have not been affected, and 38 have not yet reported. Of these 149 patients 76 have had grand mal epilepsy, and of these 19 patients have been fairly well controlled, 25 have not been affected, and 17 have not yet reported. One petit mal epilepsy patient is being given the drug and is fairly well controlled. Fifty-nine patients with convulsions due to organic cerebral disease, such as brain injury residual, have been treated with "gemonil" also. The convulsions are completely controlled in 11 patients; in 14 they have been fairly well controlled; in 17 they have not been affected, and 17 have not yet reported. "Gemonil" is almost as effective as phenobarbital and without the sedation.

"Nuvarone" (3-methyl-5-phenylhydantoin), a new hydantoin, has not yet been released and still is undergoing clinical trial. It has been an effective hydantoin. I have treated 49 patients with this drug with the following results: Of the 28 patients with grand mal epilepsy, 5 have been kept under complete control, 10 have been fairly well controlled, and 13 have not been affected. Twenty-one patients with convulsions due to organic cerebral disease, such as brain injury residual, have been treated with "nuvarone." The convulsions are completely controlled in two patients and almost controlled in seven. There have been no results in 11 and no report from 1. In this series of cases I have found only two questionable reactions of leucopenia, with leucocyte counts of 4,000 and 3,100, respectively, and with normal hemoglobin and red blood cell counts. It is necessary to check the blood count when using any hydantoin preparation.

Diphenylhydantoin (phenytoin or dilantin®) sodium has been a most unsatisfactory drug in my experience. When it has been given in large enough doses to control or prevent seizures, there have always been reactions. In children these consist of vertigo, drowsiness or stupor, irreversible hypertrophy of the gums, rash, and/or leucopenia.

I have used phethenylate ("thiantoin") sodium in 97 cases.[20b] This drug has been much more effective than diphenylhydantoin sodium and one-third as toxic. I have had three reactions to the drug, with leucopenia and slight jaundice. In all

20a. Bradley, C.: J. A. M. A. **146**:436 (June 2) 1951.

20b. This drug was withdrawn from the market by the manufacturer.

three patients the symptoms cleared completely when the drug was discontinued. In two cases use of the drug was started again without reaction. The toxic reactions to all of the hydantoin preparations, except "nuvarone" and phethenylate sodium, have been too serious and severe to justify their continued use in my hands.

The third drug of choice in the treatment of major convulsions is phenacemide. I have used this drug in 110 cases. Of these, 46 were cases of cerebral birth-injury residual, 38 of grand mal seizures due to idiopathic epilepsy, and 2 of petit mal epilepsy. The results have been good. Seven cases of birth injury residual have been kept under control with phenacemide and 11 are under fair control. Three cases of grand mal epilepsy are under control, and nine cases are fairly well under control. The two cases of petit mal have not responded. The remaining 24 cases were due to miscellaneous causes. Phenacemide is a toxic drug which has caused liver damage and has produced psychoses in adults. In my series there has been no evidence of liver damage. There have been only three cases of questionable leucopenia and two cases of behavior disturbance which may have been precipitated by the drug.

Psychomotor epilepsy is an entity established comparatively recently by the electroencephalograph.[21] It is a most serious manifestation of epilepsy, because the behavior changes and/or psychotic manifestations may not be recognized or understood without an electroencephalogram. While psychomotor epilepsy is not common in childhood, the psychic equivalents or behavior disturbances which precede the established syndrome are not rare.[22] Until the introduction of phenacemide, in 1946, there was no drug which had any effect on this disease. Phenobarbital would often aggravate the condition in children. Phenacemide will control 50% of these cases. All behavior disturbances without recognizable basis or cause should be studied by electroencephalography.

The length of treatment of the child with convulsions cannot be definitely specified. It is better to continue treatment a year longer than necessary than stop a month too soon. In general, when the effective drug or combination of drugs is found, the treatment should be continued in that dosage for at least one year after complete freedom of convulsions, and until at least one satisfactory normal electrogram is obtained. When the gamut of anticonvulsant drugs has been run—for instance, in major convulsions, phenobarbital, "gemonil," "nuvarone," phethenylate, diphenylhydantoin sodium, and phenacemide—then combinations of two drugs are in order. The first choice is phenobarbital and phenacemide. The second combination is phenobarbital and "nuvarone." The third choice is "gemonil" and phenacemide, or "gemonil" and "nuvarone." Sometimes larger doses of phenobarbital or "gemonil" may be used with amphetamine sulfate. The hydantoins should never be combined, nor should they be used with the diones or with phenacemide.

STATUS CONVULSUS

No anticonvulsant, particularly phenobarbital and the hydantoins, should ever be discontinued abruptly. Regardless of developments it is always advisable, even in changing medications, to taper off the dosage of phenobarbital or the hydantoins. The abrupt discontinuance of these drugs may precipitate a status convulsus or

21. Rockwell, F. V.; Sherfey, M. J., and Diethelm, O.: A. Research Nerv. & Ment. Dis., Proc. **26**:573, 1947.

22. Peterman, M. G.: Am. J. Psychiat. **92**:1433 (May) 1936.

status epilepticus which is extremely serious and may be fatal. When the physician sees the child in a convulsion, he has no way of knowing how long this convulsion will continue; therefore, he must make every effort to stop the seizure as soon as possible. The treatment varies with the type of convulsion and the preliminary or temporary diagnosis (Table 1). Phenobarbital sodium, subcutaneously or intravenously administered, is the first and simplest drug of choice. If this is not effective within one hour at the most, magnesium sulfate should be administered intramuscularly or intravenously. If both drugs have failed, paraldehyde is the third drug of choice. This may be given intramuscularly—or intravenously for prompt action. If the convulsions continue, the situation has become desperate and heroic measures are indicated. This means chloroform or vinyl ether anesthesia, preferably the former. Since the appearance of Ralph Waters' book on chloroform,[23] the timid and uninformed anesthetist need not hesitate longer about giving chloroform anesthesia, particularly when the responsibility is always assumed by the physician in charge. Spinal drainage is always indicated as a diagnostic and therapeutic measure in persistent convulsions. With continued convulsions oxygen inhalation may be beneficial. A continuous intravenous drip of thiopental (pentothal®) sodium may be used.

CONCLUSIONS

The treatment of convulsions in children must be based on a provisional diagnosis until a definite diagnosis can be made. The first step in treatment must be an attempt at a diagnosis.

In febrile convulsions every means must be used to reduce the fever, but anticonvulsant drugs must also be used. Fever accelerates metabolism and precipitates a convulsion in the person with a low convulsion threshold. The anticonvulsant drugs of choice in the order of their effectiveness are: phenobarbital, "gemonil" (5,5-dimethyl-1-methylbarbituric acid), phenacemide, "nuvarone" (3-methyl-5-phenylhydantoin), and the other hydantoins. Bromides may be used as a last resort. Chloroform inhalation is the most effective immediate anticonvulsant available. Paraldehyde administered by mouth, by rectum, intramuscularly, or intravenously is an effective anticonvulsant. As a last resort spinal fluid may be withdrawn and replaced with air or oxygen to produce a pneumogram for diagnostic and therapeutic purposes, and as a final resort thiopental (pentothal®) sodium may be given intravenously by continuous drip.

411 E. Mason St.

23. Waters, R. M.: Chloroform—A Study After One Hundred Years, Madison, Wis., Univ. Wisconsin Press, 1951.

FATAL CONVULSIVE SEIZURES ASSOCIATED WITH CORTISONE THERAPY

Report of a Case

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CAPTAIN EDWARD H. JOHNSTON
AND
COLONEL CARL J. LIND
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STATUS epilepticus coincident with the use of either corticotropin (pituitary adrenocorticotropic hormone, ACTH) or cortisone has been reported.[1] The fatal case herein recorded, complete with postmortem examination, does not establish the cause of such untoward reactions to therapy, but it does not support the etiologic theories so far offered.

REPORT OF CASE

A 5-year-old white boy was admitted to Brooke Army Hospital for the fourth time because of rheumatoid arthritis. Details of his previous history, including the results of therapy with cortisone, have been reported elsewhere.[2]

The patient was given 300 mg. of cortisone acetate intramuscularly the first day, 200 mg. the second day, and 100 mg. daily thereafter. On the sixth day of therapy the blood pressure rose to 140/100 (Fig. 1). Because hypertension persisted, the dose of cortisone was reduced to 50 mg. daily on the ninth day. Blood pressure values as low as 120/70 were noted during the day, but at midnight the pressure was 160/100. The diastolic pressure had dropped on the morning of the 10th day and was not considered alarming, and so 50 mg. of cortisone was again administered. The blood pressure rose during the day and by midnight was 190/150. The child seemed somewhat disoriented and complained of headache. At 6 a. m. on the 12th hospital day, 24 hours after the last dose of cortisone, tremor developed in the patient's right hand. The blood pressure at this time was 160/100. At 6:45 a. m. generalized clonic convulsions developed which could not be controlled with barbiturates. The patient remained in coma and in a convulsive state from this time until he died, 14 days later. Serum chemistry values and electrolytes were completely normal, except for a blood sugar level of 316 mg. per 100 cc. shortly after the onset of his convulsions. A few hours later the value was 94 mg. per 100 cc. and remained normal thereafter. The spinal fluid contained no increase in cells, but the protein

From the Pediatric and Pathology Services, Brooke Army Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

1. (*a*) Lowell, F. C.; Franklin, W.; Beale, H. D., and Schiller, I. W.: The Occurrence of Convulsive Seizures During Treatment of Asthma with Cortisone Acetate, New England J. Med. **244**:49 (Jan. 11) 1951. (*b*) Dorfman, A.; Apter, N. S.; Smull, K.; Bergenstal, D. M., and Richter, R. B.: Status Epilepticus Coincident with Use of Pituitary Adrenocorticotropic Hormone, J. A. M. A. **146**:25 (May 5) 1951.

2. Geppert, L. J.; O'Hara, B. F., and Peat, A. C.: The Effect of Cortisone on Nutrition, J. Pediat. **39**:267 (Sept.) 1951, Case 1.

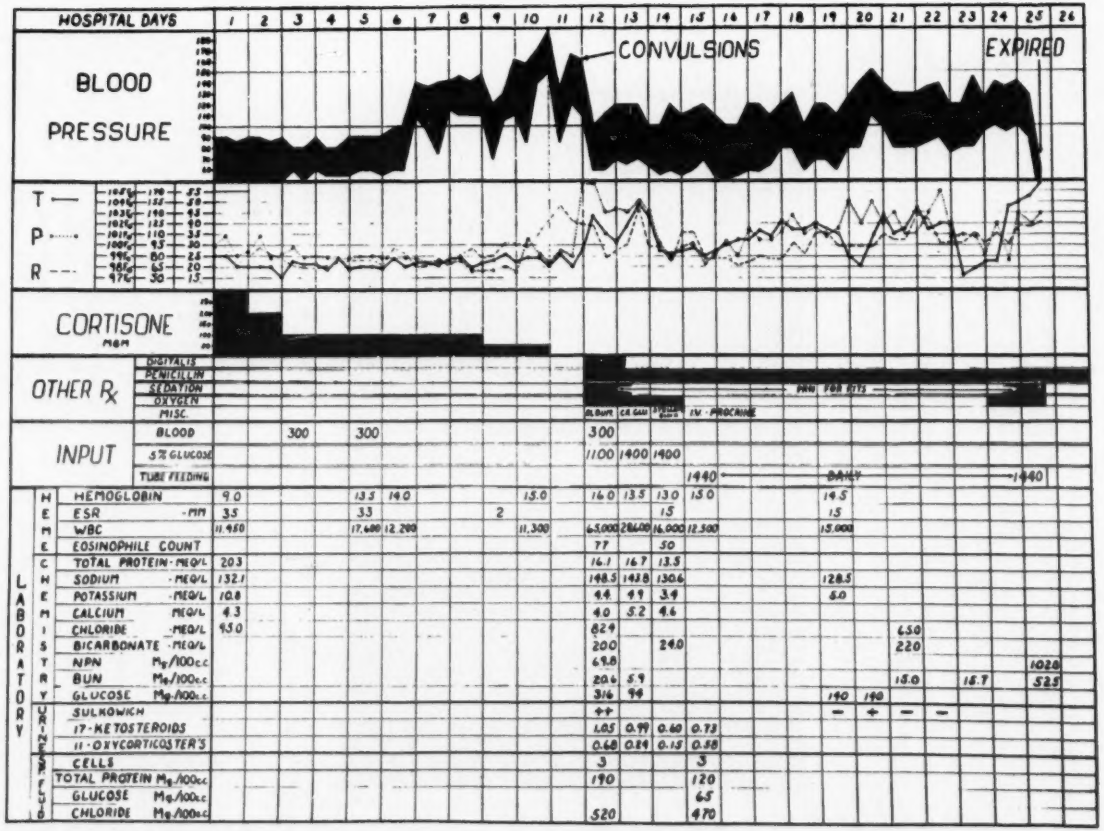

Fig. 1.—Clinical and laboratory data on a child who died in status epilepticus coincident with cortisone therapy.

was elevated to 190 mg. per 100 cc. An electrocardiographic tracing showed no evidence of electrolyte imbalance and was normal except for a rate of 240 per minute. Calcium gluconate administered intravenously had no effect on the convulsions. The blood pressure dropped to normal values shortly after the convulsions began and stabilized at 120/70. A stellate ganglion block, physiologically successful, was performed without benefit. Procaine hydrochloride was also administered intravenously with no obvious effect. Neurological examination showed the patient to be practically decorticate. An electroencephalogram (Fig. 2) showed a severely disorganized stupor record with marked suppression of cortical activity. Parenteral alimentation finally became inadequate, and the patient's serum chloride dropped to 65 mEq. as the blood urea nitrogen rose to 52 mg. per 100 cc.

Autopsy Findings.—The body was that of a 5-year-old white boy with a body length of 42 in. (107 cm.) and weight of 25 lb. (11.3 kg.). The brain showed no gross abnormality. There was generalized hypertrophy of the heart; it weighed 121 gm. (normal 84 gm.). The thymus weighed 6 gm. (normal 25 gm.). The right adrenal weighed 2.4 gm., the left, 2.1 gm. (normal 6 to 8 gm.). The adrenal cortex was narrowed, and the color was pale yellow. The

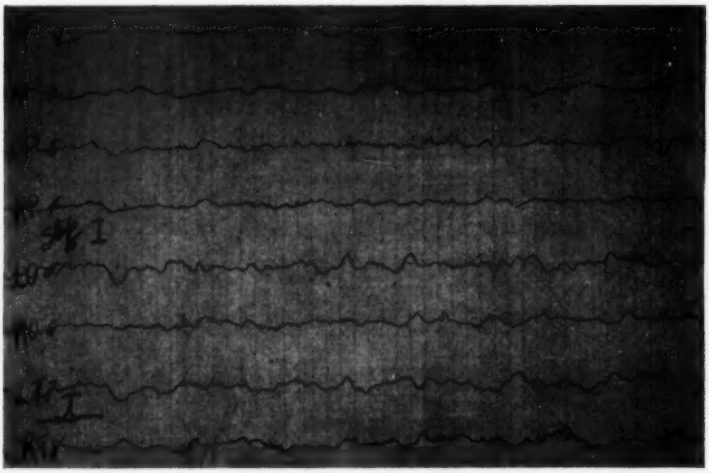

Fig. 2.—Postconvulsive electroencephalogram of patient who died in status epilepticus coincident with cortisone therapy.

liver showed a loss of lobule pattern and a yellow-red mottled appearance on cut section. The bronchi of both lungs had a faintly yellow mucoid exudate, and the parenchyma had focal areas of purulent exudate. There was nothing remarkable about the other organs.

Microscopic Findings.—In the brain there was congestion of the vessels with some edema around an occasional intracerebral vessel. All neurons were histologically normal. No hemorrhage or thrombosis could be found. The heart had a subendocardial hemorrhage like that usually seen in extreme anoxia. In addition to bronchopneumonia, there was a cluster of fat cells within a medium-sized vessel in the lung. There was marked atrophy of all the lymphoid elements of the body. The adrenals were normal except for mild atrophy. The joints showed proliferation of fibrous tissue and invasion by small noncongested capillaries.

In summary, no pathological change was noted which could account for convulsions and coma. The immediate cause of death was bronchopneumonia.[3]

3. The microscopic sections in this case were reviewed by Dr. Ernest E. Muirhead, Southwestern Medical School of the University of Texas, Consultant in Pathology, Brooke Army Hospital.

COMMENT

The rapid fluctuations in blood pressure exhibited by this patient are probably explained by a direct vasospastic effect of cortisone.[4] Hypertensive encephalopathy with intracranial hemorrhage seemed the most reasonable immediate diagnosis for this patient, but the spinal fluid pressure was low and no abnormalities were noted on funduscopic examination. Normal serum calcium values and therapeutic failure with intravenous administration of calcium make tetany seem improbable. Blood sugar values were not compatible with hypoglycemia but do not exclude a failure in glucose metabolism.

In view of the absence of organic pathological changes at autopsy, a physical-chemical explanation for convulsive seizures coincident with cortisone or corticotropin therapy seems most reasonable. Significant changes in the electroencephalogram were reported in 13 of 15 patients treated with corticotropin.[5] Conversely, corticotropin has been reported to have anticonvulsive properties for epileptic patients.[6] The suggestion has been made that certain of the central nervous system "toxic side-effects" of corticotropin administration, including changes in the electroencephalogram, may be due to potassium depletion.[7] This patient had no evidence of hypopotassemia; the serum potassium was normal; an electrocardiographic tracing showed no evidence of electrolyte imbalance; previous balance studies had indicated this patient to be in positive potassium balance under a similar regimen, and the patient was receiving 3 gm. of potassium chloride daily. Sodium intoxication may have been a factor, since there was some elevation of serum sodium and the patient had gained 1,500 gm. An intracellular sodium shift would have to be postulated.

The cause of death in this case was terminal bronchopneumonia. We have no etiologic explanation for the precipitation of the convulsive seizures. Dorfman and co-workers [1b] reported three cases of status epilepticus coincident with the use of pituitary adrenocorticotropic hormone. No significant elevation of blood pressure was noticed in any of these patients, but there were electroencephalographic abnormalities and the spinal fluid protein was increased. One of these patients had widespread brain damage one year later. Stickney [8] mentioned a 4-year-old boy treated with corticotropin for acute leukemia who went into coma and died, although the blood pressure was normal and the electrolyte pattern undisturbed. At autopsy the brain showed degenerative changes similar to the anoxic lesions seen in flyers. In contrast, our patient showed no degenerative changes at autopsy, although the spinal

4. Forsham, P. H.: Vascular Effects of Electrolytes, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, Blakiston Company, 1951, Vol. 1, p. 192.

5. Hoefer, P. F. A., and Glaser, G. H.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy: Electroencephalographic and Neuropsychiatric Changes in 15 Patients, J. A. M. A. **143**:620 (June 17) 1950.

6. Klein, R., and Livingston, S.: The Effect of Adrenocorticotropic Hormone in Epilepsy, J. Pediat. **37**:733 (Nov.) 1950.

7. Ransohoff, W.; Brust, A. A.; Reiser, M. F.; Mirsky, I. A., and Ferris, E. B.: The Effect of Sodium and Potassium on the Metabolic and Physiologic Responses to ACTH, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, Blakiston Company, 1951, Vol. 1, p. 160.

8. Stickney, J. M., and Bennett, W. A.: ACTH in the Leukemias, in Mote, J. R.: Proceedings of the Second ACTH Conference, Philadelphia, Blakiston Company, 1951, Vol. 2, p. 285.

fluid protein was elevated and the electroencephalogram grossly abnormal. Colonel Joseph J. Hornisher, Medical Corps, United States Army, who interpreted this electroencephalogram (Fig. 2), stated that it resembled tracings of patients who had been given too much shock therapy and left practically decorticate. Although our clinical, laboratory, and postmortem evidence is not complete, electrolyte imbalance, water retention, cerebral edema, vasopasm, or hypertension, neither individually nor in combination, seem responsible for the initiation of convulsive seizures in this case.

SUMMARY

Clinical, laboratory, and postmortem studies are reported on a 5-year-old child who expired from status epilepticus coincident with cortisone therapy.

No cause for the precipitation of convulsive seizures could be established other than the direct or indirect effect of cortisone on the cerebral cortex.

GARGOYLISM AND MORQUIO'S DISEASE

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AMONG the constitutional disturbances of enchondral bone growth, one must distinguish between disturbances visible at birth (depending on impairment of cartilaginous growth, such as achondroplasia and dyschondroplasia) and the progressive disturbances appearing after birth, in which the enchondral ossification is primarily impaired.

Whereas today the former group is well defined, the latter still presents many difficulties both in classification and in diagnosis in single cases. Recently, Cocchi [1] made a survey of more than 300 cases and separated them into three distinct categories: (1) dominantly inherited multiple enchondral dysostosis without cloudy corneae (Leri type), (2) recessively inherited multiple enchondral dysostosis without cloudy corneae (Morquio type), and (3) recessively inherited multiple enchondrial dysostosis with cloudy corneae (Hurler type).

It is not always easy to establish the line of inheritance in every case, since quite a number of cases have been reported in which the condition appeared in members of otherwise normal families.

For didactic purposes the following classification, modified from Fanconi,[2] is useful:

1. Epiphyseal enchondral dysostosis
   - (*a*) Generalized form (Ribbing disease)
   - (*b*) Localized forms [3]
2. Epimetaphyseal enchondral dysostosis
   - (*a*) Morquio's disease
   - (*b*) Special forms related to Morquio's disease, as, for instance, Leri's *pléonostéose* and Silverskiöld's disease
   - (*c*) Late form of gargoylism
   - (*d*) Early form of gargoylism
   - (*e*) Cystine disease (Debré-Fanconi-de Toni syndrome)

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1. Cocchi, U.: Polytope erbliche enchondrale Dysostosen, Fortschr. Geb. Röentgenstrahlen **72**:409, 1950.

2. Fanconi, S.: Über generalisierte Knochenerkrankungen im Kindesalter, Helvet. paediat. acta **2**:3, 1947.

3. Zellweger, H.; Giaccai, L., and Zabienska, M.: Über einen Fall von multiplen Epiphysenstörungen mit Luxationen, Helvet. paediat. acta **7**:185, 1952.

It cannot yet be decided whether the special forms related to Morquio's disease (*2b* in the classification) can definitely be separated from Morquio's disease, since there are few known cases.[4] It may be that in the future cases now belonging to this subgroup will be considered as instances of pure Morquio type or even Hurler type, as shown in our first case.

The present paper is concerned with the difficulties in the differential diagnoses of abortive and late forms of gargoylism. The fully developed picture of gargoylism is characterized by the following groups of symptoms:

(*a*) Epimetaphyseal dysostosis or dysostosis-dysdesmosis syndrome: short growth; stunted trunk, with lumbar kyphosis and deformities of the sternal bone; short and sometimes distorted extremities; short, broad, and stubby fingers; large, sometimes scaphocephalic skull, with a prominent forehead and bulging parietal bones, and reduced mobility of the articulations (claw hands), or, in other cases, increased mobility of the joints. X-ray signs are listed in the table.

(*b*) Signs of lipid or, according to Lindsay,[5] glucoprotein storage: hepatosplenomegaly, cloudiness of the corneae, progressive mental deterioration, abnormal granulations in the white blood cells and the bone marrow.

(*c*) Accessory signs: gruesome gargoyle face, hypertrichosis, flabby skin, umbilical hernia, tendency toward frequent upper respiratory infections, etc. The full picture of gargoylism has been thoroughly described many times.[6]

When all these manifestations are present, it is easy to recognize a case of gargoylism. However, there exist quite a number of cases in which there are only traces of the storage syndrome. Recently Ullrich and Wiedemann[7] have described a late form of Hurler's disease in a patient with normal intelligence, and normal liver and spleen, in whom only cloudy corneae revealed the presence of the storage syndrome. This form shows skeletal deformities more similar to Morquio's disease, except that the diaphyses of the long bones are rather enlarged and the maturation of the carpal ossification centers is delayed. In eight out of nine cases which have been reported, the patients were mentally normal.

On the other hand, Jervis[8] observed seven abortive cases in which only some of the symptoms of the storage syndrome could be found, such as hepatomegaly, splenomegaly, or the typical gargoyle face, but in all seven cases the corneae were clear and translucent. Jervis reviewed 148 cases from the literature and found the corneal clouding present in 88 cases; the mental deficiency was lacking in 11, the

4. Aegler, O.: Kann der Morbus Morquio vom Gargoylismus als Morbus sui generis abgetrennt werden? Ann. paediat. **176**:159, 1951.

5. Lindsay, S.; Reilly, W. A.; Gotham, T. J., and Skahen, R.: Gargoylism: Study of Pathologic Lesions and Clinical Review of 12 Cases, Am. J. Dis. Child. **76**:239, 1948.

6. Fairbank, H. A. T.: Gargoylism, J. Bone & Joint Surg. **31 B**:302, 1949. Caffey, J.: Pediatrics X-Ray Diagnosis: A Textbook for Students and Practitioners of Pediatrics. Surgery & Radiology, Ed. 2, Chicago, Year Book Publishers, Inc., 1950. Zelke, H.: Gargoylism, Ann. paediat. **177**:355, 1951. Notter, G.: Lipochondrodystrophie (Hurler's Syndrome), Acta radiol. **32**:439, 1949.

7. (*a*) Wiedemann, H. R.: Zur konstitutionellen Dysostosis enchondralis: insbesondere zur Hurlerschen und Morquioschen Krankheit, Ztschr. Kinderh. **66**:391, 1949; (*b*) Zur Spätform der Pfaundler-Hurlerschen Krankheit, Helvet. paediat. acta **4**:77, 1949.

8. Jervis, G. A.: Gargoylism (Lipochondrodystrophy): Study of 10 Cases, with Emphasis on Formes Frustes of Disease, Arch. Neurol. & Psychiat. **63**:681, 1950.

spine changes in 21, and the hepatosplenomegaly in 26 cases. In these abortive and late cases, it is not always easy, sometimes it is even impossible, to differentiate between gargoylism and Morquio's disease. Several authors [9] have tried to establish a differential diagnosis on the basis of X-ray manifestations.

The signs listed in the table are by no means typical, since in the literature are described cases of Morquio's disease with the bony changes of Hurler's disease and vice versa. We can only say that the symptoms tabulated under gargoylism speak more in favor of this disease and that symptoms tabulated under Morquio's disease speak more in favor of the latter disease. Yet, on the other hand, according to Wiedemann, the roentgenological signs of the late form of Hurler's disease are very similar to those seen in Morquio's disease.

In the earliest phase of gargoylism, i. e., in early infancy, the roentgenological bone changes are different from those in the later phase, since there are generalized

X-Ray Signs in Morquio's Disease and Gargoylism

Region	Morquio's Disease	Gargoylism
Sella turcica	Normal	Enlarged, shoe form
Vertebral bodies	Platyspondyly with irregular epiphyseal plates	Hook form with beak-like protrusion of anterior edge, especially marked in the second and third lumbar vertebrae
Long bones	Normal diaphysis	Enlarged diaphysis tapering toward metaphysis
Epiphysis	Small, irregular, ill-defined and fragmented	Bigger than in Morquio's disease
Carpal ossification centers	Normal or delayed maturation	Delayed maturation
Ribs	Normal	Spatulated, oar form

rarefaction and metaphyseal spreading, cupping, and spurring which were suggestive of active rickets or hyperparathyroidism (Caffey).[10]

Whether in the late form of Hurler's disease the lipid or glucoprotein storage is confined to the corneae, or whether later hepatosplenomegaly and cerebral symptoms will occur, is at present not known.[11] There are, however, cases in which the skeletal disturbances can be noticed early, whereas the storage symptoms appear later, as for instance in the cases of Scharff and Schinz.[12] In these cases, the cloudiness of the corneae could be observed only between the 28th and 40th year of life. Grebe described a family with epimetaphyseal dysostosis in which the oldest sibling, aged 30 years, showed corneal cloudiness, while the two younger siblings, 7 and 24 years old, presented only the bone symptoms. The delayed appearance of the storage syndrome may be illustrated by our cases 2 and 3.

REPORT OF CASES

CASE 1.—H. P., born June 5, 1942, was observed at the Children's Hospital in Zurich. There was no consanguinity of the parents. The father is an odd fellow, with fixed ideas, and is distrustful. Both parents have normal body proportions, normal joint mobility, and normal bones.

9. Wiedemann.[7a] Zellweger, H., and Schaichet, M.: Zwei Fälle von Dysostosis Morquio (zur Differentialdiagnose gegenüber Dysostosis multiplex), Helvet. paediat. acta **3**:208, 1948.

10. Caffey, J.: Gargoylism: Prenatal and Neonatal Bone Lesions and Their Early Postnatal Evolution, Bull. Hosp. Joint Dis. **12**:38, 1951.

11. Wiedemann, H. R.: Personal communication to the authors.

12. Cited by Caffey.[10]

H. P. is an only child. The pregnancy and delivery were uneventful; his birth weight was 3,300 gm. He did not start to walk and to speak until he was 2½ years old; at 5 years he was still wetting his bed. When he was 2 years old, the parents were aware for the first time of the delay in mental and physical development, and claw fingers were observed at this time.

On physical examination at 5 years, the boy showed signs of slight mental retardation, a deep coarse voice, indistinct speech, and a reduced vocabulary. He was quite observant but very odd and retarded and negativistic, with frequent temper tantrums. His body length was 115 cm. (normal 106 cm.); the length of arms was 46 cm.; the length of his legs 56 cm.; his head circumference 53 cm.; and his weight was 24.6 kg. (normal 19 kg.). His body growth was stunted, and he had fair thick and strong hair, flabby skin, a clumsy nose, pouting lips, and sunken root of the nose; all the teeth of the first dentition were present but very small (microdontia). The neck was short, with the hair line far down the neck. There was an umbilical hernia, but the internal organs were normal; the spleen and liver could not be felt. Slight muscular hypertonia was present, and the mobility of all the joints was markedly reduced, with the fingers fixed in flexion contraction and pes equinus. The abdominal reflexes and knee jerks were decreased.

The complete blood count, prothrombin, and coagulation and bleeding times were normal. The nonprotein nitrogen, inorganic phosphates, calcium, protein, albumin-globulin ratio, total and free cholesterol, and alkaline phosphatase were normal, and the Wassermann reaction was negative.

On roentgenograms the skull appeared big and clumsy, and the lateral view showed a square-shaped skull. The cranial base was rather short, the sella turcica normal, and the frontal and sphenoid sinuses not yet developed.

The vertebral bodies were distorted and slightly bigger than in normal controls of the same age, and the upper and lower surfaces of the vertebral bodies were convex. The second lumbar vertebra was slightly hook-shaped anteriorly, and the spinous processes were distorted. Oar-shaped ribs and short, and stunted clavicles were present.

The long bones were very large and showed cylindrical-shaped diaphyses. The transverse diameter of the middle of the ulna, radius, and humerus was nearly twice that of the normal control of the same age. Although the cortex of the bones was nearly normal, the medullary canal was much wider than normal. Some epiphyses were normal or slightly larger and others definitely smaller than normal. Distal epiphyseal lines of the ulna and the radius were oblique. The changes were more pronounced in the upper than in the lower extremities.

The pelvis corresponded to a normal one, but the several various protuberances were more irregular than in a normal person.

Four small ossification centers of the wrist were present. The metacarpal and phalangeal bones were shorter and wider than in a normal child. The epiphyses of the phalanges were very small.

This case was reported in 1948 as a case of *Pléonostéose Léri*,[13] with photographs of the boy and x-ray pictures.

This patient was again examined in the spring of 1951, by which time he had become completely idiotic and uttered only a few monosyllabic words. Physical examination at the age of 9 years disclosed increased muscular hypertonia, hyperactive reflexes, liver palpable 3 finger-breadths below the costal margin, spleen palpable 2 fingerbreadths below the costal margin and cloudy corneae. In the peripheral blood, the majority of the lymphocytes contained a large amount of large basophilic granules; the monocytes and granulocytes were normal (Figs. 1 and 2). No double refraction was seen in the unstained slide.

The x-ray changes were similar to those taken at the age of 5 years, except that the hook form of the second lumbar vertebra was somewhat more pronounced but still not so well marked as in other cases of Hurler's disease.

In the bone marrow, fine to coarse granulations in macrophages, osteoblasts, and lymphocytes were seen. A specimen of the liver was taken for biopsy, and it showed normal organization

13. Zellweger, H.: Ein isolierter Fall von Pléonostéose Léri, Helvet. pediat. acta **3**:199, 1948.

of the liver lobules. The liver cells were rather large, and even in the unstained slide, fine needle-shaped inclusions could be seen. In the Sudan-stained slide, many fine and coarser droplets were shown. The fat droplets were not doubly refractive. The glycogen content of the liver cells was normal.

Résumé of Case 1.—At 5 years, only slight mental retardation and skeletal changes were present. At the age of 9 years, it had become quite obvious that this

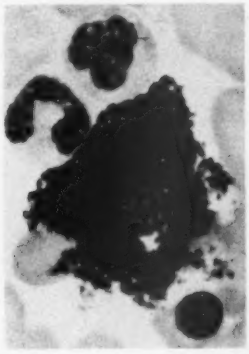

Fig. 1 (Case 1).—Lymphocytes in peripheral blood of patient at age of 9 years. The lymphocyte is full of coarse dark violet granules (May-Grünwald and Giemsa's stain), which can be seen better in Figure 2.

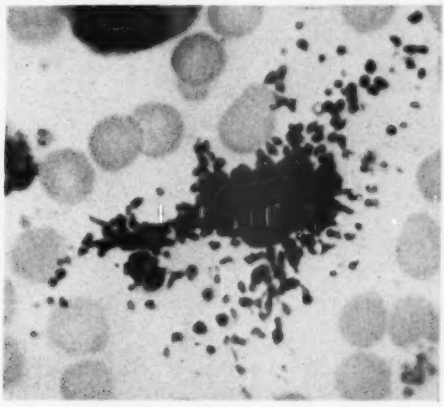

Fig. 2 (Case 1).—Burst lymphocyte in peripheral blood of patient at age of 9 years. Dark violet granules are scattered all over the slide; therefore their shape and size can be seen clearly.

was a case of gargoylism in which the symptoms of the dysostosis-dysdesmosis syndrome were present in early childhood, whereas the symptoms of storage disease developed only between the fifth and ninth years of life. Unfortunately, we did not pay enough attention to the presence or absence of granules in the peripheral blood during the first period of hospitalization, but the granulation at the age of 9 years was so impressive that it seems unlikely that it could have been overlooked during earlier examinations.

We recently had the opportunity to examine two siblings of consanguineous parents. Both children showed a severe epimetaphyseal dysostosis. The older one shows a typical gargoylism, but the younger shows only a cloudy cornea without any other symptoms of storage disease. The family is of Syrian origin. The maternal grandmother and the father of the patients are first cousins. An older sibling, a girl of 10 years, is apparently normal.

Case 2.—Bashar A. W. A., a 9-year-old boy, born after a normal pregnancy and delivery was noticed at birth to have scoliosis. The first tooth was seen at 9 months. The patient sat at 1 year and walked soon thereafter. He had measles at 5 years and a vague history of malaria. The child was "well" until the age of 3 years, when he gradually started to show disproportionate growth of the skull, enlargement of the ends of the long bones, protrusion of the anterior chest,

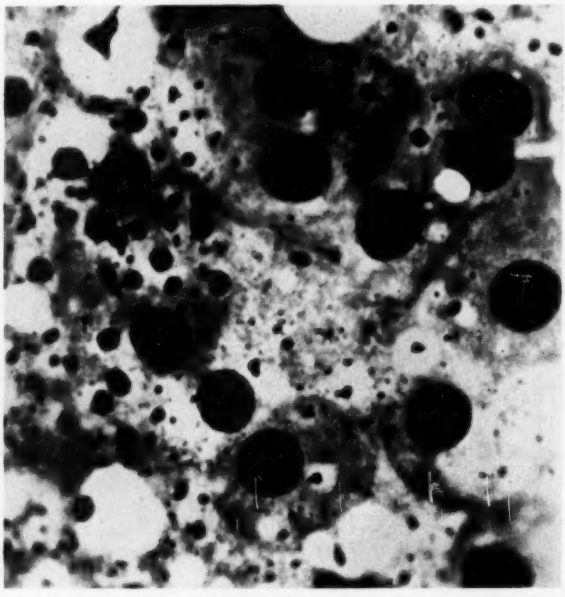

Fig. 3 (Case 1).—Bone marrow showing dark granules in reticular cells. Size of granules is bigger than in peripheral blood.

kyphosis and genu valgum. At the age of 5 years, this child was seen by Dr. Takkieddine, in Damascus. No hepatosplenomegaly, no mental impairment, and no cloudy corneae could be observed at that time. The bone changes became progressively more marked until one year prior to admission, when he was unable to walk.

Physical examination at the age of 9 years showed a crippled dwarf with stunted trunk and comparatively long extremities. His height was 91 cm. (normal, 128 cm.) and his weight 17 kg. The head was large, with a circumference of 54 cm. The frontal bones were prominent, and the facial features were coarse, with thick lips and a hypertrophic chin. The teeth were underdeveloped, the patient only having three incisors and the four first molars of the second dentition. The visual acuity was not tested, but the corneae on both sides were hazy, and slit-lamp examination showed fine deposits throughout their thickness. No blood vessels were noticed in their substance. The fundi were not properly visualized on account of the corneal cloudiness. The neck was very short, with the head sinking into the chest. The latter was

also short and had a marked kyphosis at the level of the lower thoracic region, while there was a prominent sternal boss protruding anteriorly. Harrison's groove was present. The heart had a soft systolic murmur, and the lungs were clear. The abdomen was bulging, with the umbilicus nearer the symphysis pubis than the sternum. The liver was palpable 3 fingerbreadths below the costal margin, and the spleen not palpable. The child was unable to stand. The extremities were rather long, with thickened joint regions and enlarged epiphyses of the long bones. The

Fig. 4.—(Upper Pictures) Bashar A. W. A. (Case 2) at 9 years of age. (Lower Pictures) Hazar A. W. A. (Case 3) at 2½ years, showing marked angular kyphosis when sitting.

upper arms were of normal length. The forearms and hands were short. The joints presented a state of hyperlaxity. The hands were deviated toward the ulnar side (flag hand). The hip and knee joints could be extended only to an angle of 160 to 170 degrees, while flexion was unimpaired.

The skin was extremely loose (cutis laxa). The muscles were hypotonic, except in the lower extremities, where there was an adductor spasm, hyperactivity of knee jerks, inexhaustible ankle clonus, and a positive Babinski sign. Gordon and Rossolimo signs were not elicited.

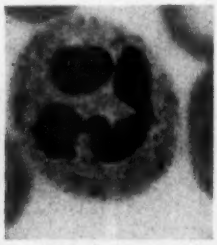

Fig. 5 (Case 2).—Leucocyte with coarse granules.

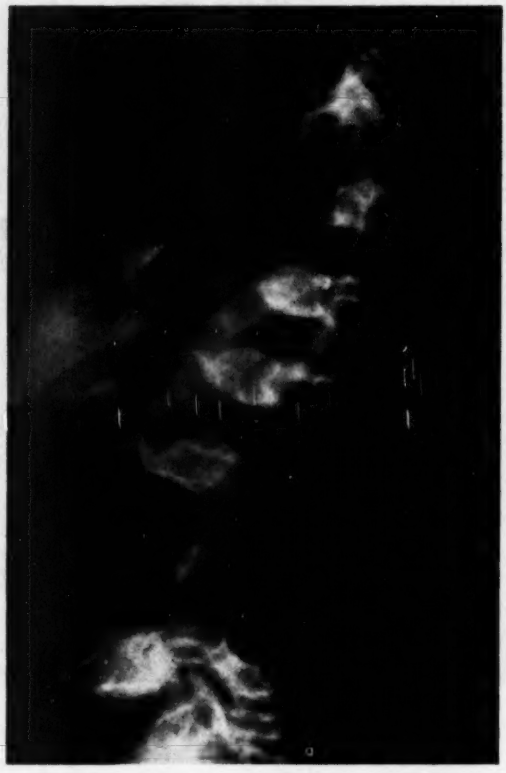

Fig. 6 (Case 2).—Wedging of lumbar vertebral bodies with anterior beak-like prolongation; dorsolumbar kyphosis.

Abdominal and cremasteric reflexes were present. Tendon reflexes of the upper extremities were elicited and the Hoffmann sign was positive. There was some dysarthria, and, while no painstaking mental tests were done, it was our impression that mental development was slightly retarded.

Laboratory Findings.—Red blood cells numbered 5,290,000, and white cells 9,000 with polymorphonuclear lymphocytes 30%, lymphocytes 68%, and large monocytes 2%. The blood calcium level was 10.55 mg. and phosphorus level 4.8 mg. per 100 cc. Alkaline phosphatase was 7.53 Bodansky units. The urine and stools were normal.

Sternal puncture was done, but the material obtained contained blood mainly, and the smear, stained with Wright's stain, showed granules in 50% of the polymorphonuclear cells. The granules were large and distinct, varying in number from one to five, scattered in the cytoplasm. They had a deep violet color (Fig. 5).

A bone biopsy specimen was taken from the left radius, and the description of the report follows: "Sections show the tissue to be composed of cartilage and adjacent bony trabeculae.

Fig. 7 (Case 2).—Oar-like deformity of ribs.

The cartilage in some areas shows ossification with precipitation of lime salts. One area of the cartilage shows destruction of the chondrocytes, and the hyaline matrix shows acidophilic granules.

"The periosteum is slightly thickened and shows no special lesions. The bone marrow stroma between the trabeculae is of the fatty type with very little hemopoiesis. Toward the cartilage there is what appears to be a mild lymphocytic infiltration."

Roentgenological Findings.—A systemic examination of the whole skeleton revealed the following changes.

The spine in the lateral view (Fig. 6) was markedly S-shaped because of a rounded kyphosis involving the lower dorsal and upper lumbar segments, with compensatory accentuation of the physiological lumbar lordosis. All the vertebral bodies of the lower dorsal and lumbar spine were markedly deformed, some of them (lower dorsal) being biconvex in outline and some others (lumbar) showing a marked wedging with an anterior tongue-like prolongation. The vertebral bodies were not homogeneous in density, and their bony structure had a blurred appearance. The outline of the epiphyseal surfaces was clear-cut. The disc spaces were all widened, especially in their anterior portion.

The ribs (Fig. 7) had a nearly horizontal course; their posterior arch was thin, whereas the anterior arch was broad and expanded, giving the ribs a characteristic spatular or oar-like appearance.

In the upper limbs the distal ends of the long bones were splayed out, and all the metaphyses and epiphyses showed a markedly irregular sometimes eaten-out, contour, and their bony structure was quite disorderly. The shafts were rather thick, though their bony structure was normal. The ulna and radius showed a volar bent, and the hand (Fig. 8) was markedly deviated toward the ulna. The nuclei of ossification of the carpal bones were very small and irregular in shape and structure. There was about a three-year delay in the time of appearance of the

Fig. 8 (Case 2).—Flag-like deviation of hand; stubby metacarpal and phalangeal bones; irregular and delayed ossification of carpal nuclei, and spotty calcifications are visible throughout carpal region. Tapering lower end of ulna and flaring-out of lower end of radius.

ossification nuclei. The metacarpal and phalangeal bones were plump, tapering toward their distal ends (the four lateral metacarpals also tapered proximally), and their bony trabeculation was coarse and blurred.

The pelvis was elongated, with a figure-8-shaped outline of its brim and with a widely gaping ischiopubic junction. The acetabula were broadened and showed a jagged outline.

The femoral heads were flattened, small, irregularly calcified, and were displaced laterally and upwards in respect to the acetabular cavities. The skeletal changes in the lower limbs were of the same type as those of the upper ones, but they were, as a whole, slightly less pronounced. The knees (Fig. 9) showed valgus deformity and both femoral and tibial epiphyses revealed irregular stippled calcification.

The skull was moderately oversized, with a comparatively narrow basis and a prominent frontal bone. Apart from this, the skull showed no abnormality, and the sella turcica was regular in size and configuration.

The over-all maturation of the skeleton, as judged from the appearance of the ossification nuclei of the epiphyses and short bones, was markedly delayed, the elbows and hips lagging farther behind normal than the carpal bones did.

CASE 3.—Hazar A. W. A., a 2½-year-old girl, is the sister of Bashar A. W. A. (Case 2). The pregnancy and delivery were normal. Her appearance at birth was normal. Her first tooth

Fig. 9 (Case 2).—Genu valgum; flaring-out of lower end of femoral shaft; stippled calcification of epiphyseal nuclei with frayed-out outline of epiphyses.

was seen at 6 months. The patient walked at 10 months and talked at 18 months. At 6 months she had severe pneumonia, and soon after her recovery her mother first noticed that the head was gradually enlarging and a forward sternal protrusion was appearing. Later on, slight lordosis, thickening of the ends of the long bones, and flat feet appeared. The mother stated that the brother (Case 2) was in much better condition when he was of the present age of his sister.

Physical Examination.—The child was thin, with slight kyphosis, pigeon chest, and knock-knees, and was able to talk and walk. She appeared to be of average mentality. Her height was 82 cm. (normal, 87 cm.). Her weight was 10.5 kg. The head was large, the lips were thick and the chin was prominent. The eyes are apparently clear, but by slit-lamp examination

the right cornea showed several opaque patches in the substantia propria, while the left cornea looked normal. The fundi were clear on both sides. The neck was rather short. The chest had a prominent forward protrusion in the upper sternum, and some kyphosis was noticed while the patient was in the sitting position. There was a marked Harrison groove, with eversion of costal margins, a wide subcostal angle, and a noticeable rosary. The lungs and heart were normal. No liver and spleen enlargement could be felt. The extremities showed thickening at the joints, especially marked at the wrist. There was a certain degree of genu valgum and pes planus. The skin was hyperplastic. The muscles were hypotonic, the joints were loose, and the tendon reflexes were present.

Laboratory Findings.—The red blood cell count was 3,820,000; the white blood cell count was 21,500. The hemoglobin content was 75%, and the patient had an intercurrent infection with diarrhea, which responded to sulfadiazine.

Examination of the blood smear in this case also revealed the same granules in the leucocytes as in Case 2. About 70% of the polymorphonuclear leucocytes contained from one to six distinct granules scattered in their cytoplasm. The granules were small and of deep violet color, not refractile, and did not resemble eosinophilic or toxic granules.

The value for serum calcium was 10.2 mg., for phosphorus 3.8 mg., for urea nitrogen 14.5 mg., and for glucose 71 mg. per 100 cc. The alkaline phosphatase was 2.5 Bodansky units. A sternal puncture was unsuccessful and yielded mainly blood.

Roentgenological Findings.—The skeletal changes in this girl bore in their general features a close resemblance to those found in the case of the older brother. They were, however, less pronounced and not so extensive.

The spine (Fig. 10) showed a slight rounded kyphosis with maximum of curvature at the level of the first lumbar vertebra. The vertebral bodies were oval-shaped, and some of them (upper lumbar) exhibited tongue-like protrusions at their anterior edges. The outline of the vertebral bodies was smooth and clear-cut. All the disc spaces were widened.

The ribs showed, to a less degree, the same broadening of the anterior arch as in the previous case.

The shafts of the long bones (Fig. 10) were somewhat plump and flared out at their extremities. Also in these patients, skeletal changes were more pronounced in the upper than in the lower limbs.

The skull was regular in size and configuration, and the sella turcica showed normal outline and size.

The skeletal development as a whole was slightly retarded, especially as far as the size of the epiphyseal nuclei and of the short bones was concerned.

Résumé of Cases 2 and 3.—In two siblings of a consanguineous Arab family, the typical signs of epimetaphyseal dysostosis with roentgenological changes of Hurler's disease were found. Contractures were lacking in the younger child. The older child similarly showed hyperlaxity and muscular hypotonia of the upper extremities, whereas the mobility of the knees and the ankle joints of his lower limbs was reduced.

Symptoms of storage disease were marked in the older child: mental retardation, spastic paraplegia, hepatomegaly, cloudy corneae, and abnormal granulations in the leucocytes of the peripheral blood. This child had a typical gargoyle face. In the smaller child, the gargoyle face is not yet developed. The only manifestations of storage disease in Case 3 are at present very fine deposits in one cornea, detectable only by slit lamp, and the same abnormal granulations in the leucocytes as in Case 2.

Without slit-lamp examination and without knowing the older brother, we would have been inclined to consider this child as having Morquio's disease, although the skeletal x-ray findings were more suggestive of Hurler's disease. But, as mentioned before, many authors agree that roentgenologically the two diseases cannot be distinguished.

The observation of these two cases may give an explanation why in some publications [14] both Hurler's and Morquio's disease have been described as occurring in the same family. It is hard to believe that two relatively infrequent inherited diseases would appear in the same family.

In all the three cases, the epimetaphyseal dysostosis appeared in the first year of life, whereas marked symptoms of the storage syndrome became manifest only later; in Cases 1 and 2 apparently only after the fifth year of life, and in Case 3 at the age of 2½ years. Only in Case 3, by slit-lamp examination, visible clouding corneae, and the granulation of leucocytes were the only evidences of Hurler's

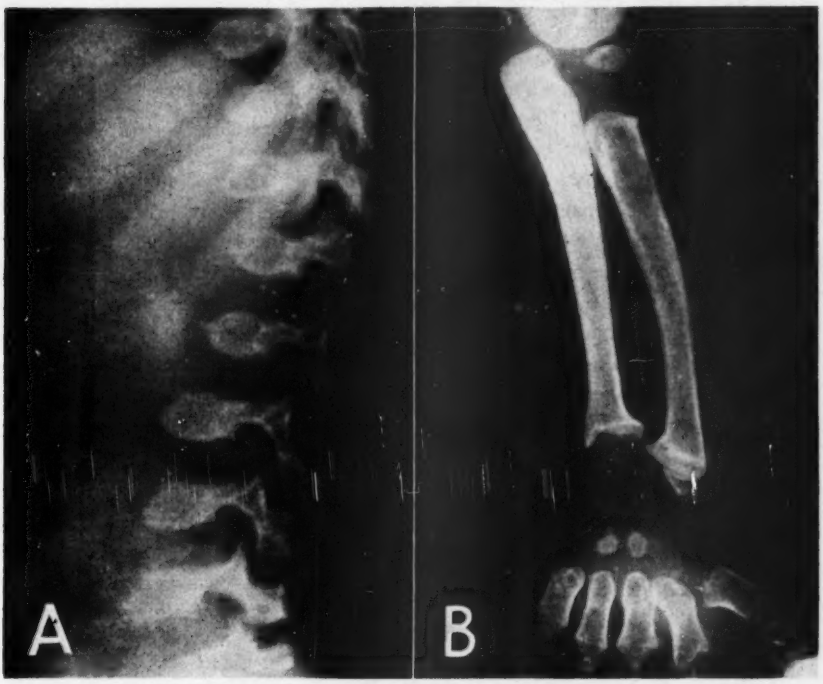

Fig. 10 (Case 3).—*A*, oval-shaped vertebral bodies with beak-like (first and second lumbar vertebrae) or tongue-like (12th dorsal vertebra) protrusion of their anterior edge; slight rounded dorsolumbar kyphosis. *B*, plump curved shafts unequally developed in length and slightly splayed-out at distal ends; stubby metacarpal bones; moderate delay in maturation of ossification nuclei.

disease. These facts indicate that in every epimetaphyseal dysostosis, a slit-lamp examination and a careful search for particular granulations in the white cells should be made. Reilly,[15] and later on Reilly and Lindsay,[16] found granulations in the

14. Bocker, E.: Zur Erblichheit der Dysostosis multiplex, Ztschr. Kinderh. **63**:688, 1943.

15. Reilly, W. A.: The Granules in the Leukocytes in Gargoylism, Am. J. Dis. Child. **62**:489, 1941.

16. Reilly, W. A., and Lindsay, S.: Gargoylism (Lipochondrodystrophy): Review of Clinical Observations in 18 Cases, Am. J. Dis. Child. **75**:595, 1948.

white blood cells of several of their Hurler disease cases. In the first publication, coarse, dark, pink to violet granulations were found with Wright stain not only in the polymorphonuclear leucocytes but also in lymphocytes and monocytes. In the cases published later, only the leucocytes were affected. In two cases of Brugsch,[17] the same granules were found in all the white blood cells, except the plasma cells. Gasser and Zellweger [18] found in three patients (one case is identical with Case 1 of the present paper), abnormal granules in the lymphocytes of the peripheral blood but not in the leucocytes and monocytes. In the histiocytes and reticular cells of the bone marrow, in reticular cells of the spleen, liver, and brain coarse granulations were present (see the photographs of Gasser [19a]). One of these patients revealed similar granules in the smears of various organs at autopsy.[19b] In Cases 2 and 3, the granulations were not so obvious and were confined to the segmented leucocytes. Most interesting are the findings of Alder.[20] In 1937 he described a special constitutional pseudotoxic granulation anomaly of two siblings, 7 and 9 years old. Not until several years later (1945) could signs of severe epimetaphyseal dysostosis be observed, but no other signs of storage syndrome (mental deficiency, hepatosplenomegaly, cloudy corneae) were present. Alder [21] considered his cases as instances of Morquio's disease and did not believe that these granules could be a sign of the storage disease. Recently similar granulations have been described by Leitner [22] in the leucocytes of a 45-year-old man with aplastic panhemocytopenia, with no bony changes or signs of storage disease. Jordans [23] describes a family in which in 9 out of 34 healthy members in three generations similar dark violet granules in the neutrophiles and blue-purple granules in the eosinophiles could be found without any other disease except diabetes in one 41-year-old woman.

Therefore, although abnormal granulations are not a constant finding in Hurler's disease, coarse granules in leucocytes and/or lymphocytes can appear as a very early symptom. However, the exact relation of these granules to the storage syndrome is not yet known, since they are also described in patients who present only bony changes and even in cases in which neither bony changes nor storage signs have been found.

17. Brugsch, H., cited by Wiedemann, H. R.: Beiträge zur Pfaundler-Hurlerschen Krankheit, Ztschr. Kinderh. **70**:81, 1951.

18. Gasser, C., and Zellweger, H.: Abnormal Granulations (Storage ?) in the Cells of Blood and of Various Organs in Dysostosis Multiplex, Exhibit Guide 94, Transactions of the Sixth International Congress of Pediatrics, Zurich, 1950.

19a. Gasser, C.: Discussion, Schweiz. med. Wchnschr. **80**:1095, 1950.

19b. Unpublished data.

20. Cited by Wiedemann.[17]

21. Alder, A.: Konstitutionell bedingte Granulationsveränderungen der Leukocyten und Knochenveränderungen, Schweiz. med. Wchnschr. **80**:1095, 1950.

22. Leitner, St. I.: Panmyelopathie bei der Alderschen Anomalie, Schweiz. med. Wchnschr. **81**:1256, 1951.

23. Jordans, G. H. W.: Hereditary Granulation Anomaly of the Leucocytes (Alder), Acta med. scandinav. **129**:348, 1947.

SUMMARY AND CONCLUSIONS

Three cases of gargoylism are reported. In Case 1, the patient's skeletal changes were well developed by the age of 5 years, but signs of storage disease could not be seen at this age and did not appear until later. At the age of 9 years, the full picture of gargoylism was developed.

In Cases 2 and 3 the patients are siblings of a consanguineous family. The former is a 9-year-old child with a fully developed gargoylism; the latter 2½ years old, had typical skeletal changes but, as far as the storage syndrome is concerned, only slight deposits in one cornea and abnormal granules of the leucocytes could be found.

Clouding of the corneae and granulation anomalies in the leucocytes and/or lymphocytes may appear earlier than the hepatomegaly and signs of brain involvement.

Therefore, in every case of epimetaphyseal dysostosis, corneal changes have to be carefully searched for with the slit lamp and the white blood cells examined for abnormal granules in order not to miss the diagnosis of Hurler's syndrome in an early stage.

In none of the three cases were the roentgenological changes described as characteristic for Hurler's disease fully represented. In Case 1, the x-ray changes were similar to those in pleonosteosis. In Cases 2 and 3 some of the characteristic signs of Hurler's disease were present, but in both cases the sella turcica was normal. Some long bones showed tapering from their ends, whereas some others showed wide flaring of the metaphyses. Therefore we hold the opinion that in most of these cases a differential diagnosis between the different types of epimetaphyseal dysostosis based only on roentgenological data is unreliable.

Synonyms for gargoylism are Hurler's syndrome, dysostosis multiplex, and lipochondrodystrophy; for Morquio's disease, synonyms are osteochondrodystrophia deformans, and Morquio type of epimetaphyseal dysostosis.

Dr. W. Shorey, Department of Surgery, helped in this study, and Dr. Sahyoun, Department of Pathology, examined the biopsy specimen.

DIAPHRAGMATIC HERNIA IN THE NEWBORN

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PARAESOPHAGEAL hiatus hernia is a congenital defect that is usually found only in adults. Its incidence in general is fairly low, while in infants or the newborn it is extremely low. The paradox of finding an adult type of diaphragmatic hernia in a newborn infant is unique. We are reporting such a case.

REPORT OF A CASE

I. S., a full-term white girl, was born on Dec. 8, 1951. She appeared normal at birth, but later, when feedings were begun, regurgitation with slight cyanosis was noticed at every attempt to swallow. Physical examination revealed good ventilation of both lungs. The heart tones were clear, and the abdomen was soft. A catheter passed into the esophagus would encounter an obstruction in the distal portion.

Chest x-rays showed a gas-filled viscus in the mediastinum to the right and dorsally from the heart. The diagnosis of diaphragmatic hernia was confirmed by an iodized oil esophagogram (Fig.).

The infant was prepared for a transabdominal repair of the diaphragmatic defect by an infusion of 100 cc. of dextrose in distilled water. She received 100,000 units of penicillin intramuscularly. The umbilical area was dressed to avoid contamination of the operative field.

With the infant under general ether anesthesia, a left upper rectus incision was made and the abdominal viscus exposed. The liver, transverse colon, and omentum appeared in their usual positions. The stomach was located in the abdominal cavity, but the major portion was herniated through an area in the diaphragm. Palpation revealed a well-defined opening about 3 by 5 cm. to the right of the esophagus. The hernia was reduced by applying gentle traction to the stomach. The esophagus was normal in length.

Mattress sutures of 00 nonabsorbable surgical (silk) suture were placed at the edges of the defect, securing the closure. The hernial sac was then plicated and sutured over the closure. The esophageal hiatus was well approximated. The viscera were reposited into the abdomen, and the incision was closed. The thorax was not entered, nor was the phrenic nerve interrupted. The infant was returned to the nursery in a fairly good condition.

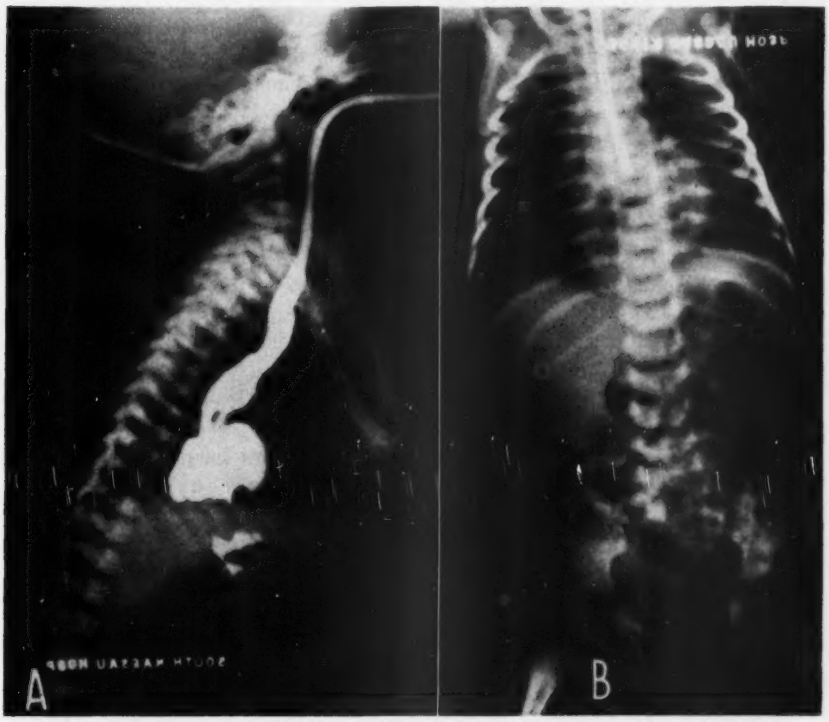
The patient received a 50-cc. isotonic sodium chloride solution infusion and 100,000 units of fortified penicillin. On the first postoperative day the infant took ½ oz. (15 cc.) of water on several occasions. The next day a milk formula was given, with fair results. On the third day the baby made only feeble attempts to swallow and frequently regurgitated some of the formula. The passage of a catheter in the esophagus encountered no obstruction. Consequently 2 oz. (60 cc.) of formula was given every two hours by gavage feedings. The baby maintained her weight of 5 lb. 4 oz. (2,380 gm.) for several days, and then it slowly increased to 5 lb. 10 oz. (2,500) on the ninth postoperative day. She was then able to take 2 oz. of formula at each feeding. She was discharged on the 13th postoperative day weighing 5 lb. 14 oz. (2,665 gm.) and nursing normally.

During the next two-week interval the baby appeared well and relished her formula. She was found dead in her crib on the morning of her 31st day of life.

A summary of the autopsy listed the occurrence of bilateral interstitial pneumonia and congestion of the abdominal viscera. Evidence of the repair of an esophageal hiatus hernia was noted. A detailed report of the diaphragmatic area revealed a normal esophagus and stomach. The diaphragm was unremarkable, there being no developmental defects. The hiatal ring was secure and the silk suture repair was intact. The apparent cause of death was suffocation.

COMMENT

Meyer [1] in 1950 stated that the esophageal hiatus closes in the 18 to 19 mm. embryo, but a permanent weak point remains. In some cases the stomach is delayed



A, lateral roentgenogram of thorax showing iodized oil in esophagus and herniated stomach. *B*, posteroanterior roentgenogram showing an air-filled retrocardiac viscus at esophageal hiatus.

in its descent and the hiatus closes about the body of the stomach or cardia. As the stomach continues to descend, the hiatus remains large, allowing space for potential herniation. The elastic membranous tissue between the hiatal ring and the esophagus and cardia will be distorted and improperly fixed, reducing the effectiveness of the barrier. Meyer feels that the enlarged hiatus is a congenital weakness which allows the development of a hernia in younger persons from increased intra-abdominal pressure or trauma and in older persons from atrophy of the diaphragmatico-esophageal membrane.

1. Meyer, H. W.: Diaphragmatic Hernia, J. Thoracic Surg. **20**:235-259, 1950.

In 1945 Harrington [2] reported a series of 404 cases of diaphragmatic hernia. Paraesophageal hiatus hernia occurred in 320 cases. In some cases a clinical history was obtained from birth. No mention was made of the range of ages. At the same time Donovan [3] reported on 17 patients who had been operated upon at the Babies Hospital in New York. One, 6 months of age and with a clinical history of three months, had an esophageal hiatus hernia. The result of the operation was satisfactory.

In 1952 Sweet [4] stated that in 111 consecutive cases of esophageal hiatus hernia the majority of the patients were between 40 and 70 years of age. Only four patients were under 40, and the youngest was 20 years of age. Miller, Parmelee, and Sanford [5] in 1939 reported the case of a 19-day-old girl who had had choking and vomiting attacks since the second day of life. At operation a paraesophageal hiatus hernia was found and repaired. Unfortunately, complications occurred which terminated the case.

Ladd and Gross [6] in 1941 reported two cases of esophageal hiatus hernia from the Children's Hospital in Boston. One patient, 9 months of age, had a transthoracic diaphragmatic repair, while the second patient, a 4-week-old baby girl, was successfully operated upon through an abdominal approach.

The early correction of the congenital diaphragmatic hernia through an abdominal approach seems justified in this case. The repair of the enlarged esophageal hiatus was satisfactory, although for a short period during the early convalescence there was partial obstruction. The final outcome of surgical treatment was successful and was not related to the patient's tragic demise.

SUMMARY

A case of paraesophageal hiatus hernia in a newborn infant, with successful repair on the second day of life, is reported. This condition is very rare, there being only four cases reported of its occurrence in infants and none of its occurrence in the newborn.

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2. Harrington, S. W.: The Surgical Treatment of the More Common Types of Diaphragmatic Hernia: Esophageal Hiatus, Traumatic, Pleuroperitoneal Hiatus, Congenital Absence and Foramen of Morgagni, Ann. Surg. **122**:546-568, 1945.

3. Donovan, E. J.: Congenital Diaphragmatic Hernia, Ann. Surg. **122**:569-581, 1945.

4. Sweet, R. H.: Esophageal Hiatus Hernia of the Diaphragm, Ann. Surg. **135**:1-13, 1952.

5. Miller, E. M.; Parmelee, A. H., and Sanford, H. N.: Diaphragmatic Hernia in Infants: Report of 2 Cases, Arch. Surg. **38**:979-989, 1939.

6. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infants and Childhood, Philadelphia, W. B. Saunders Company, 1941.

PARTIAL INTESTINAL OBSTRUCTION CAUSED BY AN INTRADUODENAL SEPTUM

Report of the Case of a Two-Year-Old Infant with Partial Intestinal Obstruction Since Birth

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THE INFREQUENCY of duodenal septa causing a partial obstruction in infants is undoubtedly a major factor in the tardiness or neglect in establishing its diagnosis. As this case well illustrates, when the symptoms are not particularly severe at birth and early infancy the diagnosis may well be masked by other abnormalities that simulate this condition. It is because of this interesting viewpoint as well as the fact that there are so few cases seen in the literature that this report is being published. The three distinct entities which could have very likely caused the symptoms presented by our patient were, interestingly enough, sufficiently plausible to have delayed the establishment of the true pathology two years.

The feeding problem in infants, when severe enough to call for hospitalization, is perhaps the most easily understandable one, as this is the one most commonly found elsewhere in the literature. Pyloric stenosis and an annular constricting head of the pancreas are quite reasonable to expect when the signs and symptoms as described are studied.

Had there been in this case a complete or more nearly complete obstruction of the duodenum, as in congenital atresia, the diagnosis would not have been so questionable. In this infant, however, the fact that the opening in the septum was large enough to allow the passage of food compatible with life and also to obstruct the duodenum only intermittently created the interesting symptomatology described in the following case.

A 2-year-old white boy was first admitted to St. Francis Hospital on Dec. 23, 1948, at the age of 16 days, with the chief complaint of vomiting. The child had been born at St. Francis Hospital, and records reveal a normal uneventful delivery with low forceps. The child was well postnatally and discharged 11 days prior to this admission. Since the child was taken home, however, he had vomited practically every feeding and the mother relates this as having been projectile in nature. The child slept well and had no diarrhea or any other troubles. Physical examination at this admission did not reveal any abnormalities; the abdomen was soft with no palpable masses or evidence of peristaltic waves. Vomiting persisted while in the hospital and the child began to lose weight. Antispasmodics did not prove to be beneficial. A gastrointestinal series was done which did not show any evidence of pylorospasm; however, there was a 50% residue of barium meal in the stomach at the end of three hours. Laboratory values all fell within normal ranges.

Chief, Fourth Surgical Service (Dr. St. John); Resident in Surgery (Dr Tamoney), St. Francis Hospital.

Because of this lack of response, the clinical impression was that the patient could well have organic pathology in the region of the pylorus and on Jan. 9, 1949, a laparotomy was performed. Careful examination failed to reveal any abnormalities of the gastrointestinal tract. The child did quite well postoperatively and was sent home on Feb. 26, 1949, retaining his formula well.

The second admission of this child was on July 25, 1949. At this time he had a rectal temperature of 104 F., and it was reported that he vomited all feedings for 24 hours. A diagnosis of acute pharyngitis was made and the patient was given antibiotics and fed parenterally for two days, after which he improved rapidly and was discharged on July 29, tolerating his formula well.

On Oct. 21, 1949, the patient was admitted for the third time, with a history of vomiting all feedings for 48 hours. Again he was fed parenterally and hydrated, and attempts were made at oral feeding. Allergy to milk and other foods was considered but never successfully confirmed. The child was now 10½ months old and retarded both physically and mentally. In view of this a neurosurgical evaluation for possible brain injury, including an encephalogram, was carried out. The impression obtained from the encephalogram was reported thus: "The record does not show any focal cortical lesion of any specific epileptogenic potential. There is unusual absence of spindles during sleep which may be related to a diffuse immaturity of the cortex."

The child was discharged on Nov. 16, 1949, after he tolerated feedings well for four days. A celiac diet supplemented with vitamins was prescribed, and he improved considerably on this.

The child was readmitted for the fourth time at the age of 13 months. He was not creeping yet and was small for his age, and examination substantiated definite physical and mental retardation. The chief complaint again was protracted vomiting; however, a moderate amount of abdominal distention was noted. The child was hydrated, and a gastrointestinal series was done, revealing an obstruction in the region of the third and fourth portions of the duodenum. Barium passed through to the colon, however, although marked dilation of the first portion of duodenum was noted.

In view of the clinical and x-ray impression of obstruction, the patient was operated on four days after admission. At laparotomy several adhesions were found from the liver to the second portion of the duodenum, release of which immediately reduced the distention of the first portion of the duodenum, and the bowel became completely collapsed. It was noted at this time, however, that this portion of the duodenum was completely surrounded by the pancreas but was not obstructed by it.

The patient did quite satisfactorily after the operation and was discharged on Feb. 21, 1950, retaining his feedings well.

The patient's fifth and final admission was on Nov. 11, 1950. He was now 2 years old and still underdeveloped for his age. The child had been vomiting for seven days prior to this admission. He had had no bowel movements in three days and had moderate abdominal distention. A gastrointestinal serial study was again carried out revealing a mechanical obstruction of the duodenum. The possibility of an intrinsic duodenal diaphragm was suggested by our x-ray department.

On Nov. 21, laparotomy was again performed in view of the intestinal obstruction with the possibility of adhesions, intraduodenal diaphragm, or annular pancreas being considered as the etiological factors. When the peritoneal cavity was entered, the small intestine, stomach, pylorus, and first portion of the duodenum were found bound densely with adhesions to the under surface of the right lobe of the liver. Careful dissection of these produced considerable doubt as to the possibility of their causing any obstruction. Further exposure revealed the previously found annular head of the pancreas, but this likewise did not seem to be the obstructing factor, and it was decided to examine the duodenum, the first portion of which was seen to be very large and dilated.

When the duodenum was opened, an obstructing membrane was found just beyond the portion where the previously mentioned annular head of the pancreas was noted. This septum was firm and had a very small opening in the middle which just barely admitted a small probe or the smallest catheter. This septum was removed, and a duodenoduodenostomy was performed. The anastomosis was performed about 1 in. (2.5 cm.) away from the pylorus. Duodeno-

duodenostomy, instead of an attempt merely to resect the septum, was performed with a twofold purpose: First, in the event that the septum recurred or scarring from its removal caused a constriction we would have a bypassing route. Second, if the annular head of the pancreas progressed, this segment of duodenum that could be obstructed would also be bypassed. It did not appear feasible to sever the ring portion of the pancreas because complications such as the possibility of cutting through pancreatic ducts or accessory pancreatic ducts with the danger of pancreatic fistula in this child whose tissues were already poor from undernourishment seemed likely. This child had a very satisfactory postoperative course and since discharge has made tremendous strides in regaining physical and mental development. The patient is now a normal and healthy child 3 years of age, having had no recurrence of the original symptomatology.

COMMENT

The size of the ostium of the septum is undoubtedly well related to the age of the patient when the diagnosis is made. Ladd and Gross [1] give the ages for 22 of their patients as running from the first week in life to 9 years, with the majority of them being in the first three weeks. They also well illustrate the embryological basis of these septa, showing how faulty development in this process gives rise to this condition. They point out the failure of the epithelial concrescences, which give rise to the solid stage of the intestinal tube in the embryo, to disappear completely during development, leaving this diaphragm of tissue. In their experience this diaphragm has been in the duodenum in over half of these cases, with the second commonest site being the ileum, and this is in keeping with other cases which have been reported. Also it is interestingly noted that usually only one such septum is found, in contrast to cases of congenital atresia, in which more than one lesion is not uncommon.

SUMMARY

A case of intraduodenal septum causing partial obstruction is presented, showing how the vagueness of symptoms and the similarity of this congenital abnormality to other conditions as well as the infrequency of incidence may result in a delay of diagnosis.

1. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941, Vol. 4, pp. 44-52.

IODIZED OIL ASPIRATION IN THE NEWBORN

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DURING roentgenoscopy of the esophagus in newborn infants, with use of iodized oil, we frequently observed the presence of the oil in the trachea and the bronchial tree. This finding in apparently normal infants could conceivably be confusing in the diagnosis of abnormalities of the laryngoesophageal region. Concern about this phenomenon prompted us to carry out further studies.

METHODS AND MATERIAL

The group consisted of 100 healthy newborn infants in ages ranging from 12 to 24 hours. They were examined in the supine position with a standard fluoroscopic-roentgenographic unit; those studied within the first 12 postnatal hours received no feeding of any kind. After a preliminary roentgenoscopic survey of chest and abdomen, the infants were fed varying amounts of chloriodized oil (iodochlorol®) warmed to body temperature, a standard feeding bottle and nipple being used. The act of swallowing was carefully observed, and the opaque medium was followed to the stomach. Spot-film roentgenograms were made of all unusual findings.

Patients who aspirated radiopaque material were reexamined at successive 24-hour periods until aspiration ceased. Infants who aspirated chloriodized oil were restudied, barium sulfate and water mixtures being fed under the same conditions.

RESULTS

Although each chloriodized oil bolus traversed the hypopharynx and entered the esophagus without delay, a small amount remained in the laryngeal area until successive acts of deglutition cleared the larynx of opaque material. In 13% of our cases, the bolus divided at the larynx, with the greater part of the bolus entering the esophagus and the remainder passing into the trachea (Fig.). This finding was infrequently noted on the first swallow but was usually noted on the third or fourth bolus of medium. The amount of material aspirated by the abnormal group seemed to bear a direct relationship to the vigor with which the feeding was taken. Careful observation showed that the flow of iodized oil into the trachea was direct and not the result of regurgitation.

Of the 13 infants who aspirated iodized oil within the first 12 hours postnatally, 4 continued to aspirate, as shown by repeat studies in the 12 to 24 hour period. Two

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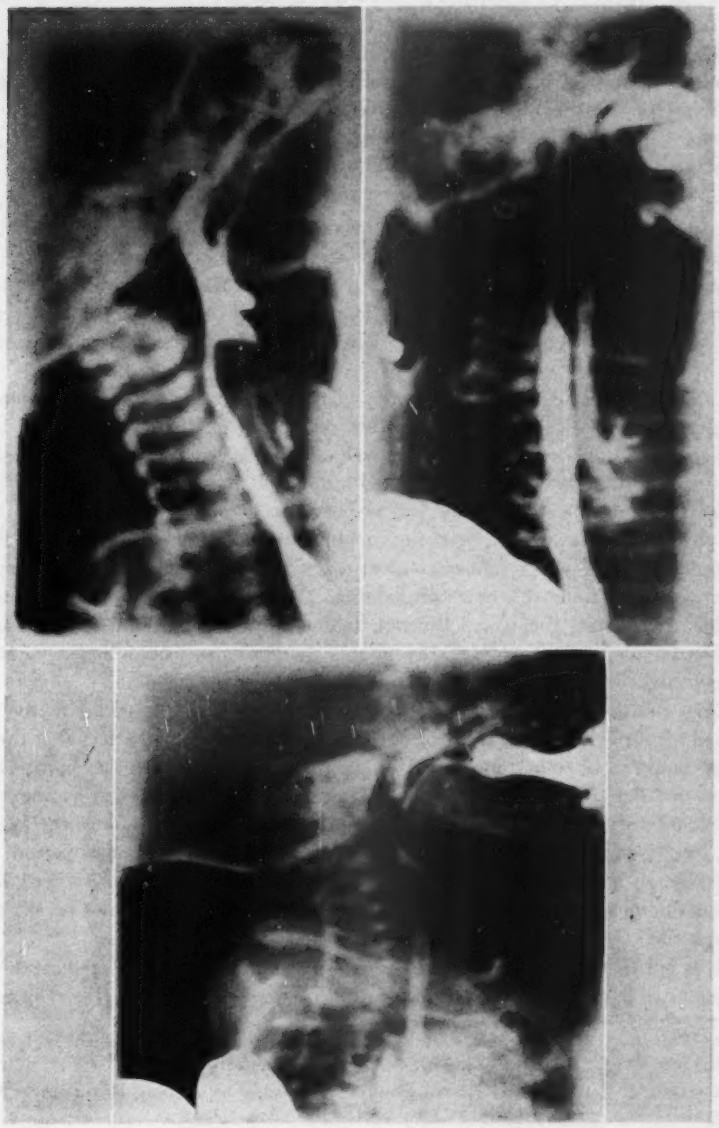

Spot-film roentgenograms of three patients, illustrating tracheobronchial aspiration of chloriodized oil.

infants continued to aspirate beyond 144 hours. The study was discontinued at this point.

In our study, when a barium mixture was substituted for chloriodized oil there were no instances of aspiration observed.

Review of the infants' and mothers' case histories showed no correlation between the results obtained and analgesia, anesthesia, type of delivery, instrumentation, time of respiration, labor time, parity, birth weight, sex, color, or complications of pregnancy. There were no feeding problems or neonatal difficulties in this group of infants.

COMMENT

It may be postulated that the phenomenon observed above is influenced by the competency of the swallowing mechanism and the type of opaque agent used. One or more of the following factors may be involved: (1) immaturity of the swallowing mechanism in the newborn; (2) low surface tension of the radiopaque medium used, and (3) functionally or anatomically defective swallowing mechanism of a permanent nature.

In favor of the theory of immaturity of nervous mechanism are the findings of Wiggers,[1] who associated the rapid heart rate noted in infancy with vagal underdevelopment in the newborn infant, as well as relative reduced gastrointestinal peristalsis and low gastric hydrochloric acid output. It has been accepted that one of the most important roles of the vagus nerve is to maintain the reflexes in the pharynx and larynx which produce coughing, swallowing, and gagging. Flagg [2] showed a loss of tone and failure of vocal cords to go into spasm on direct laryngoscopy in asphyxia in the newborn infants. A recent study by Miller [3] further emphasizes the fact that vagal function is not fully developed in newborn infants, since on direct laryngoscopy of 154 infants there was no cough reflex in 50% of those tested.

That the low surface tension (or some other inherent property) of the chloriodized oil played a role in some of our cases is illustrated by the fact that the same infants could swallow barium sulfate without aspiration. On the other hand, Caffey [4] points out that in his experience he has noted many infants who aspirated both barium mixtures and iodized oil into the trachea and sometimes into the branchial tree, most commonly during the first few days but not limited to this period.

Although a permanent defect in the swallowing apparatus might well lead to similar findings, the fact that in 11 of our infants the finding did not persist speaks against such a factor being of importance in our study.

It is felt that the findings in this study have significant clinical application in the diagnosis of high tracheoesophageal fistula of the type described by Duken.[5] In

1. Wiggers, C. J.: Physiology of Respiration, in Abt's Pediatrics, edited by I. A. Abt, Philadelphia, W. B. Saunders Company, 1924, Vol. 3, p. 694.

2. Flagg, P. J.: Asphyxia Neonatorum: Pivot upon Which Turns Movement to Prevent Asphyxial Death, Surg., Gynec. & Obst. **67**:153-162 (Aug.) 1938.

3. Miller, H. C.; Proud, G. O., and Behrle, F. C.: Variations in the Gag, Cough, and Swallow Reflexes and Tone of the Vocal Cords as Determined by Direct Laryngoscopy in New-Born Infants, Yale J. Biol. & Med. **24**:284-291 (Feb.) 1952.

4. Caffey, J.: Personal communication to the authors.

5. Duken, J.: Congenital Esophageal Spasm, Tracheo-Esophageal Fistula and Chronic Aspiration Pneumonia in Small Child, Arch. Kinderh. **99**:208-215, 1933.

institutions where iodized oil is used for roentgenoscopy of the esophagus in infants, it is possible that an erroneous impression of a fistulous communication between the esophagus and the tracheobronchial tract may be obtained.

CONCLUSIONS

Thirteen per cent of newborn infants studied aspirated iodized oil during the first 24-hour period. This aspiration probably results from neuromuscular immaturity and from the low surface tension of iodized oil.

Iodized oil is of limited value in the early roentgenographic diagnosis of sublaryngeal trachoesophageal fistulae.

Dr. Harold E. Harrison and Dr. Laurence Finberg of the Department of Pediatrics, Baltimore City Hospitals, helped in the preparation of this paper.

Case Reports

NEUROFIBROMATOSIS

Report of Cases in Negro Subjects

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NEUROFIBROMATOSIS, often called von Recklinghausen's disease, is a well known clinical syndrome. Many articles on the subject have appeared in the literature, the report given by von Recklinghausen in 1882 being the best known.

The disease is a generalized congenital symptom complex involving predominantly the skin and nervous system [1] and often associated with mental deficiency and skeletal defects. In addition, in some cases endocrinological dyscrasia and malignant transformation are exhibited. The condition shows a strong familial tendency.

In early infancy or childhood the disease may manifest itself in the abortive type, which consists of café-au-lait spots associated with freckles or hyperpigmentation. In the typical case in the older child and adult the condition often exhibits itself as tumors of the skin or molluscum fibrosum and deeper neural tumors.[2] The five cases in this report tend to illustrate the multiplicity of findings in this syndrome.

REPORT OF CASES

CASE 1.—A. H., an 8-year-old Negro boy, was admitted to the hospital with the chief complaint of a cold and cough of five days duration. He had exhibited a chronic cough since infancy and had never enjoyed robust health. Dark spots had been present on his skin since birth.

His birth weight was 2,500 gm. He was breast-fed for one year and had received orange juice but very little cod liver oil in infancy. He walked at 14 months and talked poorly at 2 years. Schooling was started at the age of 6 years, but he never progressed beyond the first grade. At the age of 3 years, he was hospitalized for three weeks for severe measles. His hearing had always been considered poor.

On examination, the child (Fig. 1*A*) appeared to be a dull, fairly well-nourished, shy boy with a low-pitched voice and slow, incoherent speech. At this time his weight was 55½ lb. (25.1 kg.) and his height 46 in. (117 cm.). The head appeared large and exhibited frontal and parietal bossing. The optic disks were pale. The turbinates and tonsils were enlarged. Dental caries were numerous. The cervical nodes were mildly enlarged. A lumbar scoliosis was present. Numerous café-au-lait spots were noted over the trunk (Fig. 1*B*). These ranged from 0.1 cm. to 5 cm. in diameter. There was a large black nevus involving the left thigh; it began 2 cm. below the inguinal ligament and extended to halfway down the leg. It was covered with "goose pimples"

From the Department of Pediatrics, Howard University, School of Medicine and the Pediatric Service of Freedmen's Hospital.

1. Westcott, R. J., and Ackerman, L. V.: Elephantiasis Neurofibromatosis: A Manifestation of von Recklinghausen's Disease, Arch. Dermat. & Syph. **55**:233 (Feb.) 1947.

2. LeBell, I.: Von Recklinghausen's Neurofibromatosis in Children: Report of 3 Cases, Arch. Pediat. **54**:454 (Aug.) 1937.

measuring about 2 cm. in diameter. The skin of the involved area was rather elastic in texture. The subcutaneous tissues and muscles of the left thigh and hip were atrophic (disuse atrophy). A bilateral genu valgum deformity, more marked on the left, was present. There was excess to-and-fro motion in all the joints on the left side, including the hip, knee, and ankle. The left knee joint was 5 cm. lower than the opposite joint. The left thigh was rotated medially. There was anterior bowing of the left tibia. The left ankle rotated laterally, giving a valgus deformity of the left foot, which was pronated. Weight bearing was shifted to the right leg, which appeared normal. The boy walked with a limp, favoring the left leg, and stood with it abducted to a 45 degree angle. Measurements of the lower extremities revealed the left to be 7.5 cm. longer than the right.

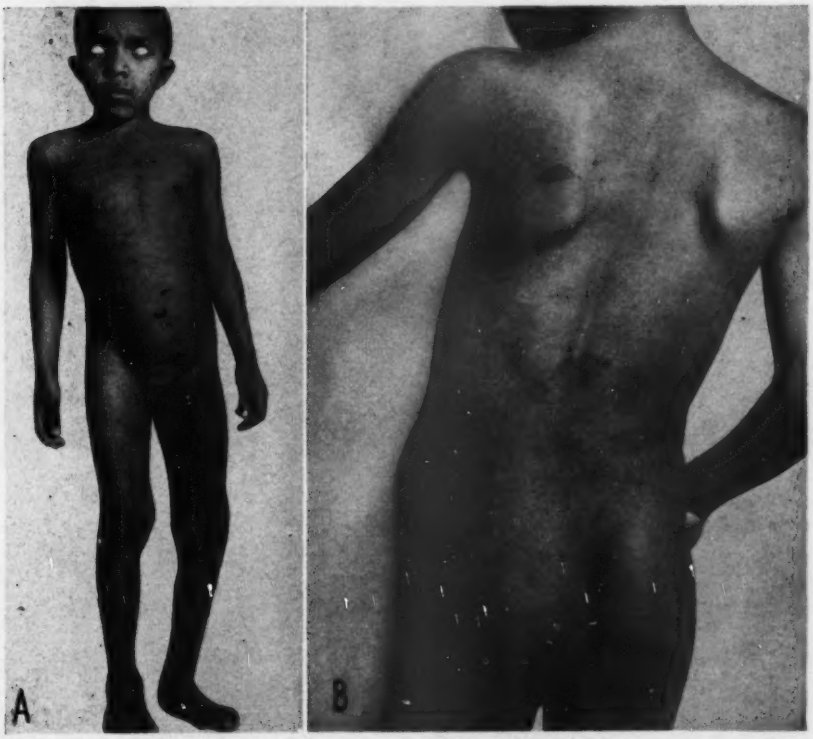

Fig. 1 (Case 1).—*A*, large black nevus involving the left thigh. The skin of the involved area was atrophic and hyperelastic. The left lower extremity was 7.5 cm. longer than its fellow. *B*, lumbar scoliosis and café-au-lait spots on the back.

Hemograms and findings on urinalysis were normal. Reactions to a tuberculin test and a serologic test for syphilis were negative. Blood chemistry studies revealed nonprotein nitrogen, 47 mg., sugar, 93 mg., calcium, 8.5 mg., and phosphorus 4.2 mg. per 100 cc., and alkaline phosphatase 5.3 Bodansky units.

Roentgenograms showed cystic bone changes and generalized osteoporosis involving the lower extremities (Fig. 2). The lumbar vertebrae were hourglass in shape (Fig. 3). The bone age (Todd standard) was approximately 7¼ years. There was bilateral clouding of the maxillary sinuses. The chest showed accentuated hilar markings. The large skull revealed prominent convolutional markings.

A psychometric examination on the Stanford-Binet scale showed that the boy's I. Q. was 56.

A biopsy of the involved skin revealed characteristic findings of neurofibromatosis.

The clinical diagnoses were (1) neurofibromatosis with skeletal changes in the spine and lower extremities, (2) mental retardation, and (3) partial deafness.

The mother (Fig. 4), aged 25 years, had typical molluscum fibrosum which developed with pregnancy of this child. However, black spots had been noted on her skin "ever since she could remember." A soft tumor had been present on her right upper eyelid since the age of 9 years. Two operations had been performed on this tumor, but there was a recurrence with time. The tumor hung down like a curtain over the right eye, which was hidden by this elephantiasis-like lesion. The mother's maternal aunt also had brown spots on her skin.

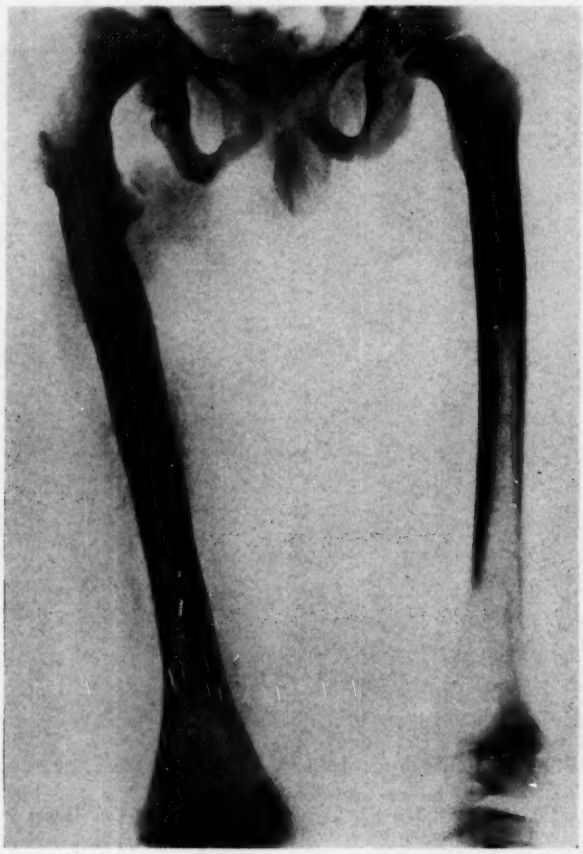

Fig. 2 (Case 1).—Roentgenogram showing osteoporosis and cystic bone changes.

CASE 2 (Fig. 5).—J. G., a Negro boy, first came to our attention at the age of 8 years. At that time he presented an enlarged, misshapen left knee with a valgus deformity which had been present since infancy, a large swelling (dermoid cyst) behind the right ear, dental caries, and black spots that had been present on the skin since birth (Fig. 5). The boy's mental development was thought to be retarded. The intraocular distance was increased.

At the age of 10 years, the patient had not progressed beyond the first grade. He had at this time a recurrent pain in the left knee and thigh. Also peculiar striations were noted in the cornea. The left side of the pelvis was atrophic (Fig. 6*A*). The genu valgum deformity had worsened,

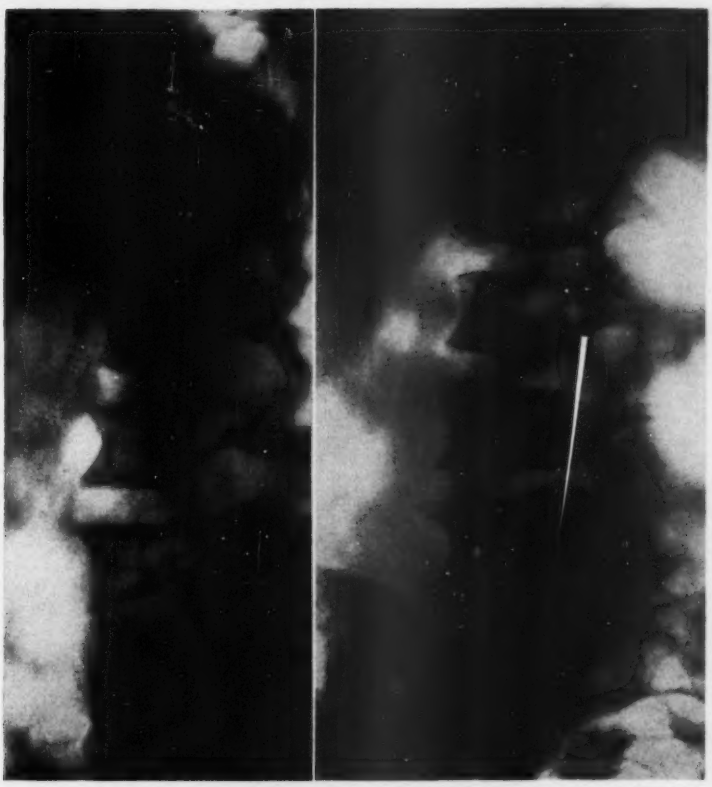

Fig. 3 (Case 1).—Roentgenograms (lateral and anterior-posterior) showing hourglass deformity of lumbar vertebrae.

Fig. 4 (Mother of A. H. [Case 1]).—Anterior and posterior views. Note the numerous small molluscum fibrosa tumors and the large elephantiasis-like lesion which obliterates the right eye.

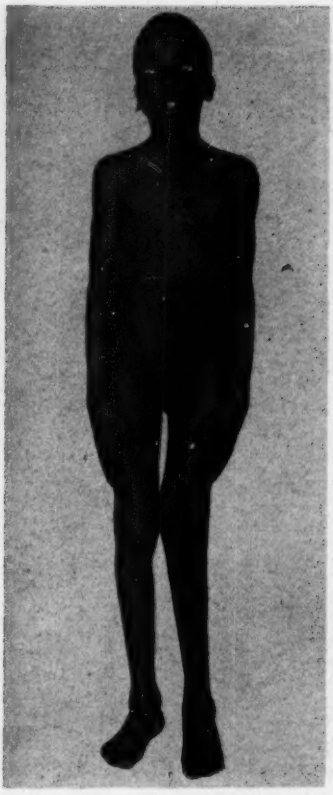

Fig. 5 (Case 2).—Photograph showing café-au-lait spots (retouched to preserve appearance of lesions) and genu valgum deformity.

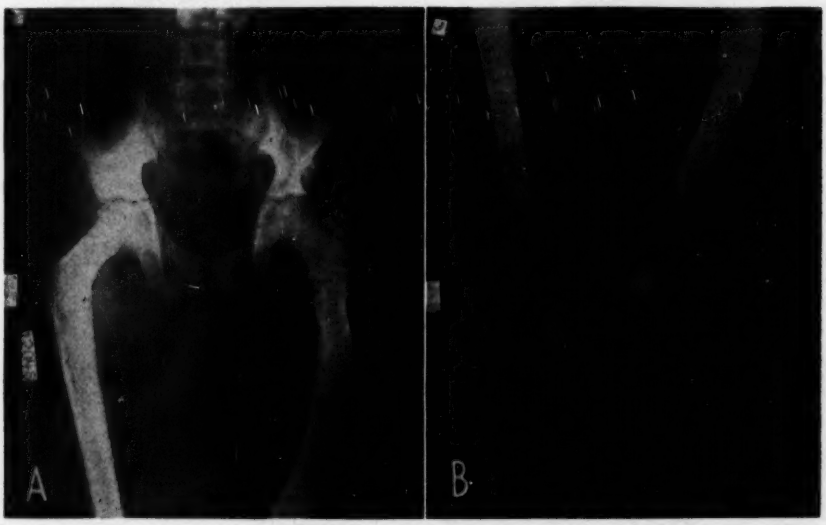

Fig. 6 (Case 2).—*A*, roentgenogram of pelvis. Notice the shortness of the femoral neck on the left where the greater trochanter is poorly developed. The ilium is atrophic on the left. Note exostosis just above the hip joint on the left. *B*, roentgenogram of femurs. Note the abnormal curvature and gross deformity on the left. The knee joints are asymmetrical.

and the left knee rubbed against its fellow. The left femur presented an anterolateral curvature with a prominence being felt in the convexity (Fig. 6*B*). The left patella was 1 in. (2.5 cm.) higher than the right. There were also exostoses on the left innominate bone, left hip, and left femur, but there was no tenderness or limitation of motion in these areas. Multiple, dark, circumscribed, elliptical spots were scattered over the skin, the average size being 2 by 1 cm. His diagnosis was neurofibromatosis with osseous deformity and hyperteleorism.

Fig. 7 (Case 3).—Photograph of posterior aspect showing disseminated pigmented spots. There is a large nevus near the popliteal area on the right.

A Stanford-Binet intelligence test showed the boy to be mentally defective, with an I. Q. of 53.

At the age of 11 years, he was hospitalized for osteoplasty of the left knee because of increasing pain in the joint. At this age he was in the second grade. All laboratory data were considered normal. He was discharged after successful healing of the surgical wounds.

Case 3.—R. G., sister of J. G. (Case 2), was first seen at 9 years of age for myopia, convergent strabismus, dental caries, and upper respiratory infection. Spectacles were prescribed, and

the other conditions were also treated. Three years later, at the age of 12 years, she was again treated for a refractive error, but, in addition, she displayed the findings of enuresis associated with lumbar spina bifida and disseminated pigmented spots over the entire body. There was a large pigmented nevus in the popliteal area on the right leg (Fig. 7). An I. Q. evaluation at this age revealed a rating of 74 on the Stanford-Binet Scale.

Diagnoses of neurofibromatosis, mental retardation, and myopia were made.

CASE 4.—W. G. (Fig. 8), a 27-year-old Negro woman, the mother of the children in Cases 2 and 3, had had multiple nodules over the entire body for 15 years. She noticed the first growth on the left elbow. Subsequently, the nodules spread to the shoulder and then became generalized

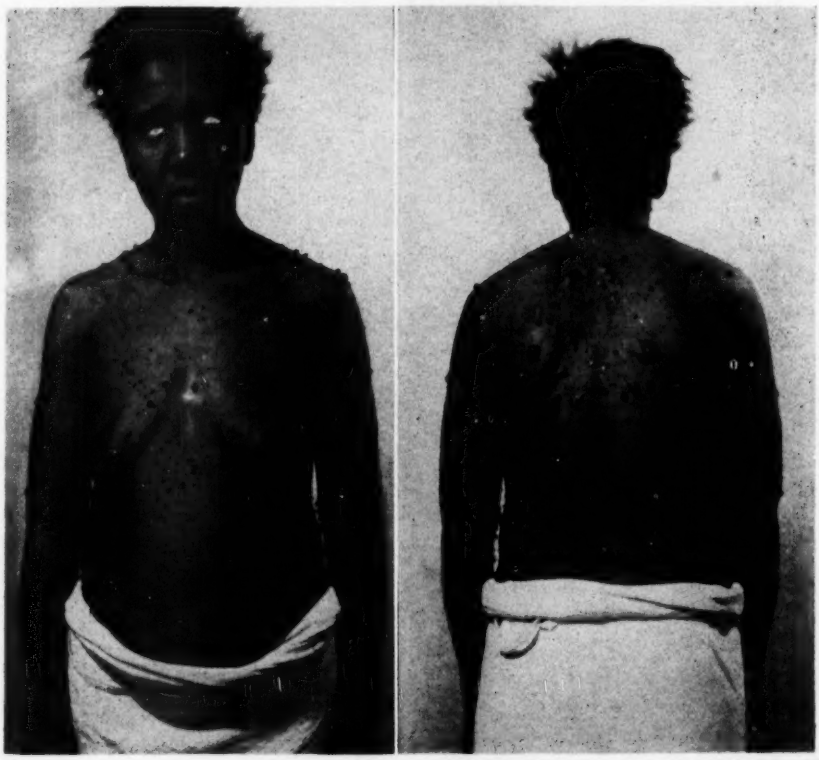

Fig. 8 (Case 4).—Photographs (anterior and posterior) showing multiple cutaneous nodules of varying size. The patient is the mother of J. G. and R. G. (Cases 2 and 3).

over the entire body. The growths were variable in size, soft, and painless. She had experienced dyspnea and palpitation on exertion since early school age. Her pupils were unequal, and the right eye was larger than the left. Dental caries, defective mentality, kyphosis, clubbing of the fingers, and depression of the reflexes were also noted.

CASE 5.—W. B. (Fig. 9) was admitted to the hospital at the age of 15 years. His complaint at that time was periodic pain in the left arm extending from the elbow to the wrist. This symptom had been present for about seven years. The left arm was weaker than the right.

The patient complained of tingling, numbness, and chilly sensations in the left arm and hand in cold weather. In walking, he did not swing the left arm but carried it stiffly at his side. Also, the left leg dragged a little on walking and became tired more easily. The patient also complained

Fig. 9 (Case 5).—Photograph showing numerous copper-colored macular areas of hyperpigmentation on the chest. The face is asymmetrical, and the left arm is smaller than the right.

Fig. 10 (Case 5).—Roentgenogram showing tumor mass in apex of left lung.

of shortness of breath, precordial pain, and palpitation. He stated that he had had no cough, hemoptysis, night sweats, or pedal edema. He slept only five or six hours a night, presumably because of shortness of breath or pain in the left arm.

He had lived in institutions all of his life and had never known a mother or a father.

Physical examination disclosed a tall thin boy in no distress. He appeared to be only fairly intelligent. His head was slightly oxycephalic. The right pupil was slightly more dilated than the left and was a bit sluggish in reacting to light. The tonsils were enlarged, and numerous dental caries were present. The lungs showed dullness and suppression of the breath sounds in the left upper posterior chest region. The heart, abdomen, and genitalia were all normal. The left arm and leg were smaller than their fellows. No sensory changes were noted in the left arm. The arm showed signs of atrophy. There was limitation of pronation and supination. The knee jerk was present on the left but absent on the right. Ankle jerks were absent bilaterally. There was a positive Babinski sign on the right side. Fibrillation was noted in the muscles of the left shoulder. Many copper-colored macules, whitish papules, and areas of hyperpigmentation (nevi) were noted over the back and chest. Just below the left nipple there was a soft tumor 2.5 by 2.5 cm. in size (Fig. 9). Pressure over this mass was painful. There were other nodules similar to the one mentioned above, but these were smaller and not painful to pressure.

The urine was normal. Blood, Hinton and Eagle tests elicited negative reactions. Many hemograms were within normal ranges. Roentgenograms of the chest revealed a left intrathoracic tumor. Other x-rays revealed a normal skull but slight scoliosis of the spine. After the lung had been collapsed sufficiently by artificial pneumothorax, the tumor mass was found to be sharply circumscribed in the upper left apex of the chest with its border extending just below the left clavicle (Fig. 10). The mass had thinned the first posterior rib; it was not connected with the lung and lay in the posterior portion of the left chest. The pathologic diagnosis on the tumor removed from the left breast was myxoid neurilemoblastoma with evidence of intracutaneous invasion probably malignant.

A permit could not be secured for removal of the intrathoracic tumor, and the child was subsequently transferred to another hospital.

A diagnosis of neurofibromatosis associated with intrathoracic neuroma and skeletal changes was made.

COMMENT

Most of the cases of neurofibromatosis in children which have been described have been instances of the abortive types, but the classic syndrome is sometimes observed. Abnormal pigmentation is generally noted in about 25% of the cases and consists of congenital freckles or nevi. Larger café-au-lait spots are also frequently noted. The shape is usually oval with no specific nerve distribution. Occasionally, depigmented areas and angiomas are the sole evidences of disease and may be present in association with other findings. The pigment is usually most abundant on the trunk, neck, and face.

Multiple tumors of the skin are most frequently encountered. They vary considerably in size. Seen most numerously on the trunk, head, neck, and hips, they can be felt partly on the skin and partly in the deep portions of the cutis or subcutaneous connective tissue. They are usually soft and nontender.

The subcutaneous neurofibromas are tumors of the larger nerves and are found most frequently on the extremities involving branches (i. e., ulnar, sciatic, and median). They are also found in the intercostals, pneumogastric, and sympathetic nerves. These tumors are usually spindle-shaped, movable, tender, and painful on pressure. The complications are caused only by their location and size, and functional disturbances are rarely encountered.

Various clinicians have given other names to variants of the three main types. These include plexiform neuromas of the nerves or plexuses; racemose neuromas,

consisting of an isolated tumor with a single pedicle, and elephantiasis neuromatosa, with thickened skin and distortion of the parts affected.

The cardinal symptoms of neurofibromatosis are enlargement of tumors and pain. Secondary associated findings frequently observed are other congenital defects, mental deficiency, scoliosis, excessive overgrowth and irregularities of the shafts of long bones, subperiosteal bone cysts, pseudoarthroses, and fibrous dysplasia.[3]

The disease is frequently familial[4] and may be associated with endocrine imbalance,[5] and muscle weakness or paralysis may be present. Frank[4a] traced the disease in five generations of one family, and Peiner[6] found 50 members affected in a family of 115. He thus concluded, as did Cockayne,[7] that the defect is a simple hereditary dominant trait. Other factors, such as cold and pregnancy,[8] have been incriminated in some cases as trigger mechanisms whereby abortive types were converted into classical cases.

There are several theories of etiology: (1) misplaced embryonal tissue, (2) overgrowth of connective tissue without involvement of nervous elements, and (3) development of tumors from the connective tissue portions of the cutaneous nerves (endo- and peri-neurium). The latter theory was first advanced by Virchow.

The disease rarely undergoes spontaneous regression, but malignant degeneration may occur. Surgical extirpation may be necessary for large, painful, or malignant growth.[9]

The cases reported here presented the following characteristic features: familial incidence, variable cutaneous lesions, skeletal changes, and mental defect. One child had malignant degeneration of a skin lesion and an intrathoracic tumor (neuroma).

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9. Phillips, H. T.; Ferri, L. B., and Morginson, W. J.: Surgical Risks Accompanying von Recklinghausen's Disease, West Virginia M. J. **28**:263 (June) 1932. Phillips, H. T.: Von Recklinghausen's Disease, Often a Difficult Surgical Problem, South. M. J. **27**:212 (March) 1934.

SUMMARY

Neurofibromatosis is a congenital, familial hereditary disease which includes abnormal pigmentations, cutaneous and deep tumors of the nerves, deformity of the skin and bones, and involvement of the central nervous system. Its chief effects are inconvenience and pain associated with the ever present possibility of sarcomatous degeneration.

During infancy and early childhood, the syndrome is often present in an abortive form characterized by café-au-lait spots, nevi, mental defect, and growth disturbances in the skeletal system. Puberty, pregnancy, aging, and periods of stress appear to be precipitating factors in the development of the classical cutaneous tumors.

The disease rarely undergoes spontaneous regression. Surgical extirpation of tumors is sometimes necessary.

SALMONELLA BREDENEY MENINGITIS

Report of Two Cases in Infancy with Recovery

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AND
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IT IS THE purpose of this paper to report two new cases of purulent meningitis in infancy due to Salmonella sp. (Type Bredeney). A review of the literature reveals that this organism has been implicated only once before as the etiologic agent in Salmonella meningitis. Both of our cases were encountered in a six-month period, and both patients recovered completely, with no neurologic sequelae, after use of chemotherapy and antibiotic agents. Case 1 represents the second youngest patient in recorded cases to have recovered from Salmonella meningitis.[1]

REPORT OF CASES

CASE 1.—A. L., a 19-day-old white boy, was admitted to the Jewish Hospital of Brooklyn on June 25, 1951, because of lethargy, anorexia, and fever. The child had been well until 36 hours prior to admission, at which time the mother noted that the baby had a "peculiar high-pitched cry." This was followed by marked anorexia and lethargy. Two hours prior to hospitalization a temperature of 38.9 C. (102.0 F.) was recorded.

The past history revealed that the child had been born at Beth-El Hospital in Brooklyn after a normal spontaneous delivery of a primiparous mother. The immediate neonatal course was essentially uneventful except that a cephalohematoma was present from birth. The birth weight was 3,210 gm. (6 lb. 11 oz.). He took 3½ oz. (105 cc.) of evaporated milk (1 part milk, 2 parts water, 5% dextri-maltose®) every four hours. Two months previously the parents, along with 20 other guests, had had a transient episode of diarrhea at an upstate New York hotel. The child's stools, however, were always normal, and there had been no vomiting or convulsive episodes.

The family history was noncontributory.

Physical examination revealed an acutely ill-appearing infant who was well developed, well nourished, and well hydrated. A high-pitched cerebral cry was noted. The weight was 3,780 gm. (7 lb. 14 oz.), the temperature 38.9 C. (102.0 F.), the pulse rate 160 per minute, the respiratory rate 30 per minute, the head circumference 35.5 cm., the chest circumference 32.5 cm., and the abdominal circumference 31.75 cm. The color was good, and the skin was clear. A cephalohematoma was present on the right side. The anterior fontanelle measured 3 by 4 cm. and was tense and bulging. The posterior fontanelle measured 1 by 2 cm. The pupils were round, regular, and equal and reacted to light. There was no nystagmus. The infant was noted to have a stare. The ear drums were clear. The pharynx and nose showed no abnormalities. There was no nuchal rigidity. The lung fields were normal to percussion and auscultation. The heart was of normal size, and no murmurs were present. The liver, spleen, and kidneys were not palpable. Kernig and Brudzinski signs were absent. The Moro reflex was absent bilaterally, and the deep tendon reflexes were sluggish. There was no spasticity.

From the Department of Pediatrics, Jewish Hospital.

1. (*a*) Metcalfe, D. C., and Wiswell, G. B.: Salmonella Meningitis in New Born, Canad. M. A. J. **62**:500, 1950; (*b*) Wood, W. H., Jr.; Mayfield, F. H., and Frisch, A. W.: Meningitis Due to Salmonella Panama, J. A. M. A. **128**:868, 1945.

The results of laboratory studies on admission may be summarized as follows:

The hemoglobin concentration was 76% (Haden-Hausser); the leucocytes numbered 28,000 per cubic millimeter, with 31% neutrophils, 35% stab forms, 30% lymphocytes, and 4% monocytes. The erythrocyte sedimentation rate was 10 mm. in one hour (Westergren). The urine was normal except for a 2+ reaction for albumin. The initial spinal fluid examination revealed a milky fluid under increased pressure. There were 2,565 white cells, with 85% polymorphonuclear forms and 15% lymphocytes. The cerebrospinal fluid protein was 240 mg. per 100 cc.,

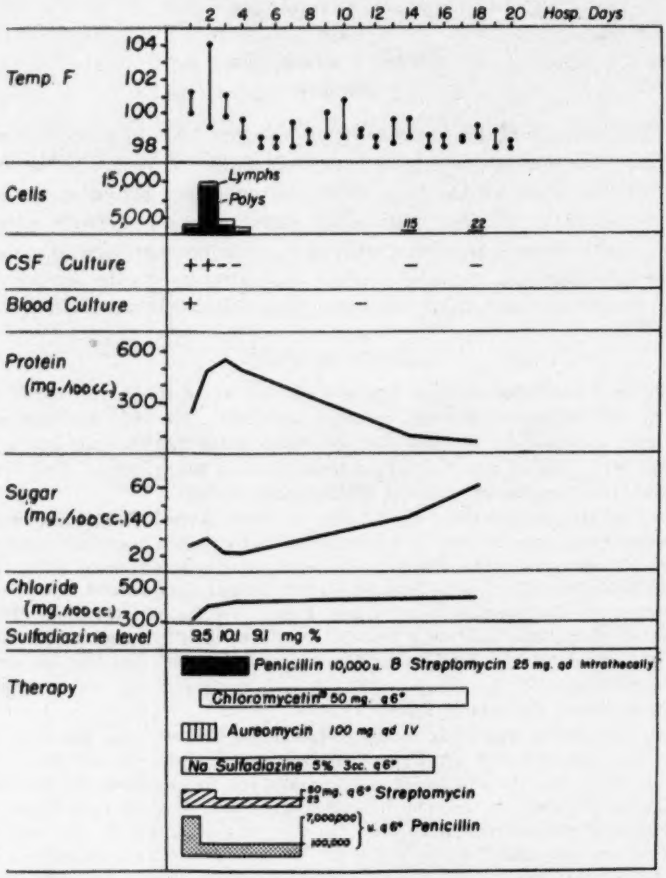

Chart 1 (Case 1).—Laboratory data and therapy for 19-day-old white boy.

the sugar 25 mg., and the chloride 303 mg. Culture of the spinal fluid and of the blood yielded a growth of a Gram-negative bacillus.

Initial treatment consisted in administration of 4,000,000 units of penicillin in aqueous solution in divided doses over a period of 24 hours; streptomycin, 200 mg. per day; aureomycin hydrochloride, 200 mg. intravenously during the first 24 hours; 5% sulfadiazine sodium solution, 12 cc. per day subcutaneously, oxygen, and penicillin and streptomycin intrathecally, 10,000 units and 25 mg. respectively. Because of vomiting, oral feedings were discontinued and fluids were given intravenously for 24 hours.

On the second day 80 cc. of fresh whole blood was given, with a rise in the hemoglobin concentration to 94%. The infant now tolerated 3 oz. (90 cc.) of evaporated milk (1 part

milk, 2 parts water, 5% dextri-maltose®) every three hours. The temperature ranged from 37.3 to 40.0 C. (99.2 to 104.0 F.). The anterior fontanelle remained tense. Examination of the spinal fluid revealed an increase in cells to 14,240, with 90% polymorphonuclear forms. The culture remained positive. Intrathecal administration of penicillin and streptomycin was repeated. Sensitivity studies on the organism revealed it to be most sensitive to streptomycin and chloramphenicol. Administration of the latter, therefore, was started in a dosage of 200 mg. per day.

Forty-eight hours after admission there was definite clinical improvement. The anterior fontanelle was flat and nonpulsatile. The Moro reflex was elicited, and deep tendon reflexes were active and equal. A smear of the spinal fluid revealed no organisms, and the culture was sterile.

There was steady clinical improvement, and five days after admission the infant appeared well. The cerebrospinal fluid remained sterile, with a fall in the white cell count. On the fourth hospital day the organism was identified as S. sp. (Type Bredeney) by Dr. Erich Seligmann, of the National Salmonella Center in New York City. Intrathecal therapy was given for a total of four days. Streptomycin and penicillin were continued in use for 7 days, sulfadiazine for 15 days, and chloramphenicol for 16 days. The infant displayed a steady weight gain from 3,780 gm. (7 lb. 14 oz.) to 4,440 gm. (9 lb. 4 oz.) on discharge. Neurologic examination on the 20th hospital day (the day of discharge) disclosed no significant abnormalities.

Other laboratory data were as follows: The hemoglobin concentration ranged from 67 to 94%, the red cell count from 2,930,000 to 4,380,000, and the white blood cells from 28,000 to 10,200 (a slight polymorphonuclear leucocytosis was present throughout the hospital stay). Findings on repeated urinalyses were normal except for a 2+ reaction for albumin on the first and second days. Results of tests for enteric agglutinins on the 1st, 4th, and 12th days were negative. Stool cultures on four occasions were negative for pathogens. A urine culture on the 10th hospital day was sterile. The nose culture grew Staphylococcus aureus, and the throat culture grew Staph. aureus and a Streptococcus of the viridans group. Enteric agglutinins on the mother's blood were negative. Stool cultures from the mother and father were negative. Further data will be found on the accompanying chart (Chart 1).

Reexamination of the patient eight and one-half months after the onset of the meningitis, on March 23, 1952, was carried out. The weight was 9,360 gm. (19 lb. 8 oz.). The head circumference was 45.0 cm. The child recognized his parents and the surroundings of his home. He stood with help and acted normally in all other respects. The neurological examination was completely within normal limits.

Case 2.—D. G., a 3-month-old white girl, was admitted for the first time to the Jewish Hospital of Brooklyn on Dec. 3, 1951, with the chief complaints of irritability and poor feeding of 24 hours' duration. The present illness began two weeks prior to admission, when the child had a slight episode of diarrhea that responded to dietary measures. Twenty-four hours before entry, at 4:00 a. m. the infant awoke crying and was extremely irritable. She took 4 oz. (120 cc.) of a whole cow's milk formula poorly. Three hours later the infant was noted to have a temperature of 38.9 C. (102.0 F.). A pediatrician who saw the child at this time noted abdominal distention and moderate hyperperistalsis. No bulging of the anterior fontanelle was noted at this time. Cremosuxidine® (a suspension of succinylsulfathiazole with pectin and kaolin) and elixir of donnatal® (an elixir containing hyoscyamine sulfate, atropine sulfate, hyoscine hydrobromide and phenobarbital) were prescribed, and the diet was restricted to clear fluids. On the day of admission the infant had a temperature of 40.0 C. (105.0 F.) and marked bulging of the anterior fontanelle was noted. She was extremely irritable. A diagnosis of meningitis was made and hospitalization advised.

The family history was negative for any familial diseases. Both parents and one sibling had recent moderately severe upper respiratory infections. There was no history of diarrhea in the family.

The past history revealed that the patient was born prematurely, weighing 2,220 gm. (4 lb. 10 oz.). The pregnancy and delivery had been uneventful, and the neonatal course was uncomplicated. The child was taking a whole boiled cow's milk formula with supplemental vitamins A and D (vifort®). No immunization had been given. The developmental history was entirely satisfactory.

Physical examination at the time of admission revealed a well-developed, well-nourished, white female infant in severe acute distress. The child was hyperactive and extremely irritable. The temperature was 39.9 C. (103.8 F.), the pulse rate 120 per minute, the respirations 30 per minute, the weight 4,680 gm. (9 lb. 12 oz.), and the head circumference 37.75 cm. The anterior fontanelle was markedly bulging and pulsatile and measured 3 by 4 cm. The skin was clear, and there were no petechiae. The skin turgor was good. There was no lymphadenopathy. The pupils were round, regular, and equal and reacted to light. The con-

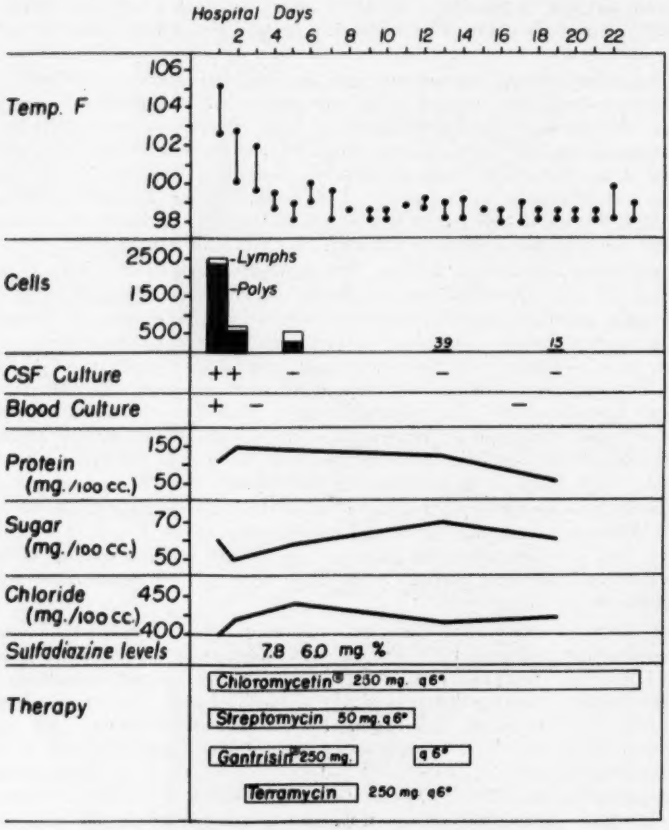

Chart 2 (Case 2).—Laboratory data and therapy for 3-month-old white girl.

junctivae were clear. The lungs were normal to percussion and auscultation. The heart sounds were of good quality, and there was no enlargement. There were no palpable organs or masses in the abdomen. The genitalia were normal. The deep tendon reflexes were active and equal bilaterally. The Kernig sign was positive. The Brudzinski and Babinski signs were not elicited.

The initial laboratory data were as follows: The hemoglobin concentration was 65% (Haden-Hausser), the red blood cell count 3,500,000, and the white cell count 12,400, with 71% polymorphonuclear leucocytes, 28% lymphocytes, and 1% monocytes. The erythrocyte sedimentation rate was 18 mm. per hour (Westergren). The urinalysis was negative. The carbon dioxide-combining power of the blood was 41.3 vol.% and the chlorides 363 mg. per cubic centimeter. Initial cerebrospinal fluid examination revealed grossly cloudy fluid under increased pressure with a white cell count of 2,500, of which 95% were polymorphonuclear leucocytes.

The Pandy reaction was 1+. The protein was 111 mg. per 100 cc., sugar 63 mg., and the chloride 399 mg. A Gram-negative organism was seen on smear of the spinal fluid.

The patient was placed on a regimen of chloramphenicol (chloromycetin®) palmitate, 250 mg. every six hours; sulfisoxazole (gantrisin®), 250 mg. every six hours, and streptomycin, 200 mg. per day intramuscularly. The child took a whole boiled cow's milk formula, was placed in an oxygen tent, and was given alcohol sponges when the temperature rose above 39.5 C. (103.1 F.).

The child was able to retain the oral medication with no difficulty. The temperature rose from 39.9 C. (103.8 F.) on admission to 40.8 C. (105.2 F.) six hours after entry and then began to drop steadily until the patient was afebrile, on the fourth day. No further temperature elevations occurred. On the second hospital day the spinal fluid was still grossly purulent but the cell count had dropped to 700 white cells. Clinically the infant appeared much improved. She ate well and became more responsive. However, the anterior fontanelle was still markedly bulging and the culture of the spinal fluid remained positive.

On the third hospital day the organism was isolated and identified, at the National Salmonella Center, New York City, by Dr. Erich Seligmann, as S. sp. (Type Bredeney). In vitro sensitivity studies showed the organism to be most sensitive to terramycin. This antibiotic was added in the form of concentrated drops, 250 mg. every six hours. The infant's clinical condition continued to improve. The anterior fontanelle was flat on the third day. There was no increase in the size of the head. On the fourth day the spinal fluid culture was sterile. One hundred milliliters of fresh whole blood was given on the seventh day, with a rise in hemoglobin concentration to 80%. The white blood cell count ranged from 10,600 to 18,900 per cubic centimeter, and the differential count revealed an absolute lymphocytosis during the course of the hospital stay. Values on repeated urinalyses were normal. The admission stool culture was negative for organisms of the typhoid-Salmonella-dysentery group. The nose culture grew Staph. aureus and diphtheroids. The throat culture grew viridans Streptococcus and Staph. aureus. Stool cultures from the patient's father, mother, and sibling were negative.

On the ninth hospital day the infant had two bloody diarrheal stools. Administration of terramycin was discontinued at this time, and the diarrhea immediately ceased. The infant gained weight steadily and weighed 4,980 gm. (10 lb. 6 oz.) on discharge. Neurological consultation just before the patient left the hospital revealed no evidence of gross cerebral damage. Electroencephalography was unsuccessful. Further data will be found on the accompanying chart (Chart 2).

Reexamination when the infant was 6 months of age revealed that the child was developing normally in all respects. The weight was 6,528 gm. (13 lb. 6 oz.). The head circumference was 40.25 cm. Neurologic examination was entirely negative.

COMMENT

Ghon [2] in 1907 first reported two cases of "metastatic meningitis" in young children with enteritis. Salmonella paratyphi B was identified as the etiologic organism in one of these cases. From 1917 to 1925 sporadic cases were reported in the literature. The first comprehensive review of the subject by Bahrenburg and Ecker [3] appeared in 1937. In 1948 Henderson [4] exhaustively reviewed the literature and added 3 cases to the 144 previously reported. None of these cases was caused by S. sp. (Type Bredeney). Statistics revealed that the course of the disease was favorably influenced by sulfonamides. Of 19 patients thus treated, 10 (52%) recovered, while of the 128 patients who received no sulfonamide therapy only 8 (6%) recovered. The prognosis was seen to be profoundly influenced also

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3. Bahrenburg, J. H., and Ecker, E. E.: Meningitis of Salmonella Group, J. Infect. Dis. **60**:81, 1937.

4. Henderson, L. L.: Salmonella Meningitis: Report of 3 Cases and Review of 144 Cases from Literature, Am. J. Dis. Child. **75**:351, 1948.

by the age of the patient and the species of organism involved. Only 1 of 49 patients less than one month of age recovered, while 17 of 80 older patients did not succumb to the disease. It is interesting to note that in the series of cases reported from 1948 to 1951 by Beene, Hansen, and Fulton [5] the mortality rate was still 82.7% (a total of 87 cases were included). Beene was of the opinion that the sulfonamide drugs did not alter the mortality of the disease.

S. sp. (Type Bredeney) was first reported in 1937.[6] Although the incidence of isolation of this organism has increased in recent years, it is still rather unusual to find this organism as a pathogen for man.[7] The rarity of occurrence of this organism may be indicated by a review of 3,000 human Salmonella infections noted at the National Salmonella Center in New York City from 1939 to 1945.[8] In only nine cases were the causative organisms identified as S. sp. (Type Bredeney), and none of them were cultured from the cerebrospinal fluid. Similar figures are found in a review from the department of animal pathology of the Kentucky Agriculture Experimental Station.[9] A total of 12,331 Salmonella cultures from human and animal sources were obtained. Of these 334 were cultures of S. sp. (Type Bredeney); however, only 34 of these were from human sources. Thirty-three of the 34 cultures were obtained from the stools (the 34th was classified as miscellaneous). The organism was first isolated from the spinal fluid in 1948.[10] We are reporting the second and third instance of isolation of S. sp. (Type Bredeney) from the spinal fluid. The organisms in our cases were also obtained from the blood. Five other cultures of S. sp. (Type Bredeney) that have been obtained from the spinal fluid have been recorded in the files of the National Salmonella Center in New York City during the last 14 months.[11] None of these cases have been reported. The genus Salmonella is comprised of many different species and types, and special diagnostic antisera are required to establish species- and type-identity. Therefore it is only at one of the National Salmonella Centers that some of these organisms can be properly identified.

In 80% of the cases recorded in the literature there was a preceding history of gastroenteritis and diarrhea.[12] This was noted to occur in Case 2. In the majority of cases the enteric agglutinin titer did not rise during or after the course of the disease. This was true in Case 1 (unfortunately, the reports on Case 2 are missing). The clinical course of the disease and the pathology are not unlike those of other forms of purulent meningitis and need no comment here. Suffice it to say

5. Beene, M. L.; Hansen, A. E., and Fulton, M. D.: Salmonella Meningitis, A. M. A. Am. J. Dis. Child. **82**:567, 1951.

6. Kauffmann, F.: New Salmonella Type (Salmonella Bredeney) and Evaluation of Antigen Tables, Ztschr. Hyg. **119**:356, 1937.

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8. Seligmann, E.; Saphra, I., and Wassermann, M.: Salmonella Infections in the United States of America, J. Immunol. **54**:69, 1946.

9. Edwards, P. R.; Brunner, D. W., and Moran, A. B.: Further Studies on the Occurrence and Distribution of Salmonella Types in the United States, J. Infect. Dis. **83**:220, 1948.

10. Schweig. K., and Cameron, P. J.: Salmonella Bredeney Meningitis in a 3 Month Old Infant, Harlem Hosp. Bull. **1**:41, 1948.

11. Seligmann, E.: Personal communication to the authors.

12. Levinson, A.; Kadison, E. R., and Diamond, J. H.: Salmonella Typhimurium Meningitis, Am. J. Dis. Child. **80**:290, 1950.

that early recognition of the disease process is of paramount importance. We attribute the good results obtained in our cases in part to the very short history in each instance.

Because of the recorded high mortality rate in Salmonella meningitis, it was thought best to treat our patients with multiple antibiotic therapy plus chemotherapeutic agents. We used streptomycin, sulfadiazine sodium (or sulfisoxazole), and chloramphenicol as the basis of our therapy. Terramycin was added for a period of six days in Case 2 because of the in vitro sensitivity studies, which showed the organism most sensitive to this antibiotic. Intrathecal therapy, although by no means routine, was also used for four days in Case 1. It consisted of penicillin and streptomycin. Clinical and laboratory improvement was prompt with the institution of the above routine. Both aureomycin [13] and chloramphenicol [14] have been used by other authors in the treatment of Salmonella meningitis with encouraging results. With the advent of these newer antibiotic agents to which the Salmonella organisms have proved sensitive we may expect a more hopeful prognosis in this form of purulent meningitis. Certainly the recovery of the two infants reported on in this paper, aged 19 days and 3 months respectively, would tend to support this view.

SUMMARY

The second and third cases of Salmonella sp. (Type Bredeney) meningitis are reported. Both patients were infants and prompt clinical and laboratory improvement followed intensive antibiotic and chemotherapeutic treatment.

555 Prospect Place.

Dr. Benjamin Kramer assisted in the preparation of this manuscript. The Department of Bacteriology of the Jewish Hospital of Brooklyn identified the organisms as belonging to the Salmonella group. Dr. Henry Leonard gave permission to report Case 2.

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Effect of Certain Hormones and Other Chemical Compounds on Experimental Poliomyelitis. Dr. Albert B. Sabin and Dr. A. Howard Fieldsteel (by invitation), Cincinnati.

The incidence and severity of the paralytic consequences of poliomyelitis are influenced by many factors in the virus and in the host. The effect of certain hormones and other chemically defined substances on the course of experimental poliomyelitis in various hosts will be described in this communication. The Lansing strain of poliomyelitis virus produces paralysis in hamsters which in the majority of instances is mild and self-limited, is occasionally transitory, and is fatal in only 40 per cent of paralyzed hamsters. A single dose of 5 mg. of cortisone administered to male baby hamsters (20 gm.) on the day of intracerebral virus inoculation increased the incidence of paralysis and converted the mild, paralytic illness into an almost uniformly severe, prostrating and fatal illness. The $L.D._{50}$ was 100 times less and the $P.D._{50}$ (50% paralytic dose) 10 times less for the cortisone-treated than for the untreated hamsters.

In adult mice both the Lansing and the MEF_1 strains of poliomyelitis virus produced a uniformly fatal paralytic disease, and a 5 mg. dose of cortisone, administered as to hamsters, had little, if any significantly reproducible effect. The peak level of virus multiplication was the same in cortisone-treated and in untreated mice. A statistically highly significant difference was, however, found in the response of cortisone-treated suckling mice. Untreated suckling mice were relatively more resistant to infection with poliomyelitis virus than adults, in that approximately 30 times more virus was required to initiate infection in them. A single dose of 0.5 mg. of cortisone given at the time of inoculation at 2 to 3 days of age brought the susceptibility of the suckling mice up to that of the adults.

In rhesus monkeys, cortisone in a daily dose of about 12.5 mg. per kilogram a day had no effect on the experimental disease produced by about 60 $P.D._{50}$ of a virulent strain of virus, but was capable of converting the nonparalytic and mild paralytic disease produced by strains of low virulence into severe paralytic infections. The latter observation was made on a sufficiently large number of animals to impart high statistical significance to the data.

Corticotropin (ACTH) in large doses (500 units per kilogram a day in divided doses) over a period of eight days had no effect whatever on the course of the experimental disease in hamsters and thus failed to duplicate the marked enhancing effect of a single dose of cortisone. This observation could be correlated with a difference in the effect of the two hormones on the metabolic functions which influence weight gain in these rapidly growing animals—the single dose of cortisone stopped weight gain for about seven days, while the repeated large doses of corticotropin had no effect or less effect on weight gain. The simultaneous administration of corticotropin to hamsters treated with cortisone did not abolish the enhancing effect of cortisone on morbidity but did delay death and reduce mortality to a certain extent.

Certain 8-aminoquinoline compounds were tested for their effect on experimental poliomyelitis in rhesus monkeys, because, after administration by stomach tube, they have been found to produce changes in certain neurone groups which are also generally affected by poliomyelitis virus. One group of these compounds was found to accelerate and aggravate the poliomyelitic process, while another was found to retard and partly inhibit it. These effects were produced on the disease resulting from infection with a virulent strain of virus on which cortisone had no effect. The retarding and inhibitory compound, 8 (3-diethylaminopropylamino) 2-methoxy quinoline (isoplasmocid), was, however, without effect on the poliomyelitic process in mice and on infection by the oral route in cynomolgus monkeys; toxicity tests indicated that it is metabolized differently in these animals than in rhesus monkeys.

DISCUSSION

DR. HORACE L. HODES, New York: I have had the opportunity of seeing the original experiments of Dr. Gregory Shwartzman demonstrating some of the findings which Dr. Sabin spoke about. I should like to add to Dr. Sabin's statistical data, which are very convincing, a brief description of the experiments of Shwartzman which first demonstrated the effect of cortisone upon the severity of poliomyelitis infection in animals.

Dr. Shwartzman made the observation that cortisone greatly increased the virulence of poliomyelitis virus for young hamsters. Untreated young hamsters had a paralysis and mortality rate of approximately 14 per cent. When they were inoculated with cortisone, the paralysis rate rose to nearly 100 per cent and most of the affected animals died.

Five milligrams of cortisone is a large dose for an infant hamster. This fact is partly offset by the fact that absorption of the amount administered apparently is very limited, at least in the preparations that Dr. Shwartzman has used. I wonder whether Dr. Sabin would like to comment on this particular point.

DR. ALBERT B. SABIN, Cincinnati: Five milligrams of cortisone does not, by itself, kill hamsters of this age. It does produce a cessation of weight gain for about six to seven days, after which they go on gaining weight as if nothing had happened. I want to stress that we cannot transpose such data to human beings.

One may rightfully ask: Is there ever a time when the adrenal gland is stimulated to put out enough cortisone to approach the 5 mg. dose used here? Is it possible that the reason corticotropin does not work is that it does not stimulate the secretion of enough cortisone to have this effect?

Creation of Synthetic Heritable Types of Hemophilus Influenzae and Interpretations.

DR. HATTIE E. ALEXANDER and (by invitation), STEPHEN ZAMENHOF, PH.D., and GRACE LEIDY, A.B., New York.

Demonstration that highly specific desoxyribonucleic acids function as genes in three different bacteriologic families—Diplococcus pneumoniae, Hemophilus influenzae, and Neisseria meningitidis—raises the probability that the same mechanism controls and can change the inherited characteristics of all micro-organisms. The increasing evidence of the similarity between the physiology of micro-organisms and that of the cells of higher organisms supports the speculation that the principles found to control the inherited characteristics of bacteria may prove applicable to inherited abnormal cells of man, for example, leukemic and neoplastic cells. The nature of the process responsible for the change in the inherited characteristics of bacteria therefore assumes great importance.

H. influenzae proved to be a highly satisfactory tool. The action of desoxyribonucleic acid which brings about a change in inheritance was shown to be not essentially different from other chemical reactions when both reagents—the susceptible cell and the desoxyribonucleic acid—were present. It was first necessary to show that only a minute proportion of the total population exposed is susceptible to transformation. This permitted the selection of a population size known to contain susceptible cells. When the two essential reagents, the desoxyribonucleic acid and the susceptible cells were present, the experimental results supported the following conclusions: The reaction between the desoxyribonucleic acid and the susceptible cell which results in change of type specificity is virtually instantaneous; it occurs in the absence of growth and a complex environment; specific antiserum is not essential. Study of the chemical nature of the transforming principle suggested that it is the desoxyribonucleic acid molecule itself which functions as a gene. The susceptible cell made up only a minute proportion of the total population exposed to desoxyribonucleic acid; it exhibited characteristics of a bacterial mutant.

Susceptibility to change in inheritance by desoxyribonucleic acid is independent of the presence or absence of the gene-controlling type-specific polysaccharide. A fully equipped type-specific population is just as susceptible to change to a new type as is the R-cell derived from that type.

In the process of studying the nature of the susceptible cell, evidence of two type-specific genes was found within the same transformed cell. Two new types of H. influenzae were synthesized. Each exhibited within the same cell genetic units controlling the type-specific polysaccharides of two different types of H. influenzae. In one types a and b and in the other

types a and d were found within the same cell. These double type-specific traits were transmitted unchanged in 99.99 + % of the population through many generations. Evidence demonstrated that the desoxyribonucleic acid controlling type ab was a different molecule from the addition of desoxyribonucleic acid molecules isolated from natural types a and b.

Not only was the ab trait of the synthesized strain transmitted unchanged through many generations, but the ab trait could be induced in susceptible cells with predictable uniformity by exposure to the desoxyribonucleic acid from type ab cells.

The results suggest that desoxyribonucleic acid action on susceptible cells brings about changes heretofore thought to occur only after the fusion of cells in sexual reproduction. Genetic material from the transformed cells representing one parent and the desoxyribonucleic acid from the other, genetically different parent were combined in the same cell. The results are consistent with segregation of the combined traits in subsequent progeny.

DISCUSSION

DR. HORACE L. HODES, New York: I wonder whether Dr. Alexander would like to speculate on the mechanism by which such cross relationships as those which exist between certain types of H. influenzae and pneumococci have come about.

DR. HATTIE E. ALEXANDER, New York: I am glad Dr. Hodes used the term "speculate." The subject is fun to dream about. When you are so completely absorbed in it, you get to the point of feeling you can explain almost anything by the interaction of desoxyribonucleic acids. On the other hand, I think you can feel fairly certain that the mechanism has been and will continue to be the basis for the origin of new species.

Dr. Stokes, we have not done any work on the virulence of these organisms. I think that only by deduction can we predict. We know that nonencapsulated H. influenzae organisms are frequently found in the nasopharynx living symbiotically with the host, whereas the incidence of type-specific H. influenzae organisms of the single type usually have some role in infection either in the past or at the time they are isolated. I think one can presume that because they are encapsulated and show type specificity they are potentially virulent.

Laboratory methods for assessing the virulence of H. influenzae, to my mind, are unreliable. They are artificial. They require suspending the organisms in mucin.

Pathological and Serological Relationships Between Canine Distemper and a Respiratory Tract Infection of Human Beings. DR. JOHN M. ADAMS, Los Angeles.

Experimental data indicate a possible direct relationship between a proved virus disease of dogs (distemper) and a respiratory tract infection of human beings (primary pneumonitis). Comparative pathological material shows a striking similarity in morphological characteristics; the staining properties appear to be identical in human and in animal tissues.

Neutralization of canine distemper virus infection in ferrets was accomplished experimentally. Infection caused by this virus in living chick embryos was neutralized by human sera and by human gamma globulin. Both in vivo and in vitro methods were employed.

The world literature on a possible relationship between the commonest respiratory disease of dogs, canine distemper, and human illness was reviewed. The former disease has been proved to be due to a specific virus.

In spite of the evidence from the morphological and the serological data, the limitations of each are such as to indicate the need for further study before the two diseases can be said to have a similar origin.

DISCUSSION

DR. AMOS U. CHRISTIE, Nashville, Tenn.: I should like to take this opportunity to congratulate Dr. Adams. I have talked to Dr. Goodpasture a number of times about this problem. I know that he has worked extensively for a long period, using his egg membrane technique, and has been unable to do what Dr. Adams has done so well, that is, produce growth of canine distemper virus on egg. The significance of this achievement is apparent, I am sure, to everybody. If the virus can be produced with regularity, the production of a vaccine is the next step. Everybody in experimental and veterinary medicine will be interested.

I should like to ask Dr. Adams, because Dr. Goodpasture will ask me, for more information as to how he handled the material when he put it on the eggs.

DR. SAMUEL KARELITZ, New York: Some time ago my colleagues and I were impressed, as were many others before us, by the similarity of distemper in the dog and measles in the child. The older literature contained reports of the occurrence of distemper in a home where a child had been ill with measles and of the occurrence of these diseases in the reverse order, suggesting a relationship between measles and distemper.

A long time ago, to test the possible relationship between the two diseases, I asked at the Rockefeller Institute that the prophylactic effect of measles convalescent serum be tested by injection of some into ferrets infected with distemper virus. I cannot give the details of the dosage of serum used or tell how many animals were used, but the report I got was that the measles convalescent serum was unsuccessful in protecting ferrets infected with distemper virus from getting distemper.

I do not mean to imply that there is any relationship between what we did and what Dr. Adams reported. I merely want to add this observation on measles convalescent serum to the gamma globulin study.

DR. WOLF W. ZUELZER, Detroit: I want to apologize for trespassing into the field of virology, but I may be able to add one small observation relevant to the subject discussed by Dr. Adams.

Recently I observed an infant whose underlying illness, reticuloendotheliosis, was presumably unrelated to the problem but who died with the clinical picture of a respiratory infection. Study of the lungs and other organs showed a giant cell pneumonitis, and inclusions similar to those of canine distemper and to those of the beautiful slides of Dr. Adams were found in the respiratory tract and elsewhere. A detailed history then established that the child had been in intimate contact with a puppy who had subsequently died of distemper. Material from the patient's lungs was inoculated into ferrets in a study made jointly by me and Dr. Cyril Stulberg, of the Child Research Center. The ferrets showed no clinical or pathological evidence of distemper, and when subsequently exposed to distemper virus from a canine source were not protected. This meager bit of evidence left us with the feeling that so-called giant cell pneumonitis of the type so beautifully illustrated by Dr. Adams is either caused by a virus distinct from that of canine distemper or else, as a more remote possibility, in passing through human beings is so profoundly modified that it loses the pathogenicity for the ferret.

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: The observation by Dr. Adams of the similarity of viral infections in dog and man remind me of a historical bacteriological situation.

After the characteristic tracheal lesion of whooping cough had been described as caused by Hemophilus pertussis, and a similar lesion produced in puppies by Mallory and Hornor, it was finally agreed that this experimental lesion could have been produced by Brucella bronchiseptica —once regarded by some as the cause of dog distemper.

Now it is interesting to hear Dr. Adams bring out the clear resemblance of a canine and a human respiratory tract infection with a viral etiology. I should like to ask him if the human disease can be reproduced in the dog.

DR. HORACE L. HODES, New York: I should like to ask Dr. Adams to discuss several technical points which he did not have time to discuss. One has to do with this: There are in human sera at least two nonspecific virus-neutralizing substances which are heat-labile. I want to ask whether the human sera he used had been heat-inactivated and if they had been, at what temperature.

Another point has to do with the gamma globulin he used. Gamma globulin as ordinarily supplied has preservative in it, an appreciable amount of phenylmercuric nitrate. I wonder whether the neutralizing action by gamma globulin which Dr. Adams observed was obtained with specially prepared gamma globulin from which preservative had been omitted.

Finally, another technical question regarding the neutralization. I wonder whether the human sera were tested against other viruses at the time they were tested against distemper virus. This point also has to do with the question of specificity. The results would be very convincing if distemper virus was the only one of two or three viruses which had been neutralized. I should also like to know how many minimum lethal doses of virus a dilution of 1 to 100 represents.

DR. JOHN M. ADAMS, Los Angeles: I should first like to express my gratitude for this discussion. I should make it very clear to Dr. Christie and others that we were not the first

to adapt distemper to eggs. Haig of South Africa was the first successfully to adapt distemper virus to chick embryos. Dr. Herald Cox, of the Lederle Laboratories, has continued to work with this virus in eggs and is now producing a successful vaccine for animals.

We have attempted passage in puppies and find them difficult to work with because of their immunity. We have used ferrets and have also worked with monkeys. I could use this three minutes to show you the rest of the slides; I just have one or two more. (The slides were shown.) These slides show inclusion bodies in pharyngeal epithelial cells from monkeys inoculated with human material. Monkeys do not normally have inclusion bodies, and these, we believe, occurred as a result of the inoculation. We carried out four successful passages from monkey to monkey.

Recurrent Swelling of the Parotid Gland. Dr. Stephen W. Royce (by invitation), San Marino, Calif.

The diagnosis of recurrent mumps, or of mumps confined to one parotid gland, no longer seems tenable. Wesselhoeft's work demonstrating the widespread invasion of the virus and Ender's studies on its antigenic properties suggest that the possibility of a second attack of mumps is unlikely. There are certain infants and children, however, who have repeated attacks of parotid swelling, perhaps as many as 10 or 12 each year for a number of years. In each instance the clinical appearance of the gland is indistinguishable from that seen in epidemic parotitis, yet the children have no other symptoms of the contagious disease. They undergo successive quarantine periods and often surgical procedures, and a good deal of unnecessary parental concern is expended before the correct diagnosis—recurrent nonepidemic parotitis—is made.

From the Babies Hospital in New York and the Children's Hospital in Boston 22 cases were studied. Each child had at least 4 attacks of parotid swelling; half of the children had over 15 attacks, and two had over 50. The results of bacteriological and mumps complement-fixation studies were investigated, and the influence of antibiotics and antispasmodics was traced.

A definite pattern was found. The attacks usually began at the end of infancy and were first unilateral. Later they become bilateral and increased in number, reaching a peak during the middle years of childhood and ceasing before adolescence.

There were no prodromal symptoms except a sense of fulness in the gland. The swelling was rapid and often complete in a few minutes.

The question of hypersensitivity and the possible role of infectious agents were investigated and suggestions made for handling the individual case.

DISCUSSION

Dr. John A. Bigler, Highland Park, Ill.: I want to compliment Dr. Royce on his paper. My associates and I have seen about 100 children with recurrent swelling of the parotid gland. Is this just a childhood disease, and does it occur in people of different races?

I have seen two adults with the same manifestations the children showed, and neither gave a history of having had swelling during childhood. I also have had the opportunity of seeing a few children who had mumps between episodes of nonspecific parotid swelling. At least, I thought the condition was mumps because of the fact that I was not able to milk any flocculent material from the gland, the course of the swelling was very much like that of mumps, and other members of the family had mumps at that time.

We have rarely seen this condition in Negro children, but I do not know whether this fact is significant.

In every case we have seen of recurrent parotid swelling we have been able to obtain Streptococcus viridans from the secretion of the gland, and yet, despite rather extensive treatment with penicillin, we have not been able to produce any shortening of the period of illness. In our experience x-ray therapy has given the best results in shortening the course of the disease and in lengthening the periods between recurrence.

We have noticed, just as Dr. Royce has, that the episodes usually seem to stop at about the time of puberty. This may be a false impression, because we have not been able to follow the children into adult life.

Suppuration occurred in three of our cases; therefore I do not think the disease is always benign. In two cases suppuration occurred on one side, and in the other it was bilateral. The same flocculent material was milked from the duct. In all three cases Streptococcus viridans was obtained from the pus from the suppurating gland.

We have never had the courage to take a biopsy specimen, but I hope that Dr. Royce can screw up his courage sometime to do so.

DR. JEROME COHEN, New York: I just want to ask a question. Is there an excess amount of saliva when the glands are massaged? I have seen this several times—when you press the gland the saliva runs out. I have also seen two children who whenever they have an allergic attack, asthma or hives have swelling of the parotids. It does seem, therefore, that in some cases the condition has something to do with allergy. I have observed one child for 10 years who now, at the age of 16, is still having recurrent parotid swelling.

DR. EDWARD C. CURNEN, New Haven, Conn.: I should like to hear further comment on the occurrence of fever and leucocytosis in association with these episodes.

DR. MURRAY H. BASS, New York: I want to say that at our hospital we happen to have had on our staff a physician who had this disease, and we also had employed in the hospital an elderly woman who had had the disease for many years. It is definitely not a disease only of childhood.

In my practice I have watched one boy who has attacks three or four times a year, who is very ill with them, who has a high fever, and who is sometimes in bed as long as six weeks. The glands have never suppurated. Bacteriological studies and virus studies by Dr. Alfred Florman failed to show anything of importance. The skin test showed that the boy previously had had mumps. Surgery was considered, but the danger of facial paralysis has inclined surgeons not to operate. This boy is now 20 years old and he is still having attacks.

DR. ROLAND SCOTT, Washington, D. C.: In relation to the possible allergic nature of the disease, I should like to ask if anyone has found eosinophiles in the secretion expressed from the gland.

DR. ALFRED L. FLORMAN, New York: My associates and I have also seen recurrent parotid swellings, and I was very glad to hear Dr. Royce point out the difficulty of differentiating this benign syndrome from illnesses which fulfill all his criteria but in which the patients have rather high titers of complement-fixing antibody for mumps.

We followed one such child for over four years, and he maintained a titer of 1 to 64 in the complement-fixation test. You will recall that normally after an attack of mumps the complement-fixation titer falls, so that by the end of two years or so antibodies are present, but at a rather low level. In the course of investigating this unusual persistence of antibody we took a biopsy specimen from the child's gland. We were unsuccessful in recovering the mumps virus from his saliva or parotid gland. Nevertheless, sialograms showed the characteristic droplet formation indicative of a chronic inflammatory reaction. The biopsy confirmed the sialogram, since there was both an acute and a chronic inflammatory reaction.

At the time we did the biopsy, we made bacterial cultures of material from the orifice of Stensen's duct and recovered a Type 19 pneumococcus. On that basis, and because of the similarity, as Dr. Royce has suggested, to bronchiectasis, we thought it might be wise to instill penicillin directly into the parotid gland via Stensen's duct. This was done the first time with the patient under ether anesthesia. The child recovered from his parotid swelling more promptly than before. He has since had many more attacks, and now these are treated by his local dentist, who injects penicillin with the child under nitrous oxide anesthesia.

DR. STEPHEN W. ROYCE, San Marino, Cal.: I was hoping that more of you would defend the concept of recurrent mumps, because the diagnosis is still undecided in my mind.

I believe that I can answer Dr. Bigler's and Dr. Cohen's questions together. First, the question of Streptococcus viridans and whether the children have excessive mucus.

My feeling is that they probably do not have excessive mucus. In fact, they may have too little mucus. The bacteria-inhibiting properties of secretions from the parotid gland are notably poor, and if bacteria are not washed away from the orifice of the duct, any kind, and perhaps most probably Str. viridans, may remain, accounting for the repeated attacks. We do not know this to be true.

Dr. Curnen, the patients who have fever usually have it only at the onset of the attack; many patients have no fever at all.

Dr. Bigler and Dr. Bass have both pointed out that this disease is not limited to childhood. There is a tendency for it to subside at adolescence, but it has been reported in adults many times.

The question Dr. Scott asked about eosinophiles may be answered this way: Some 70 years ago Kussmaul was interested in this disease and found that the plug which often blocked the duct was composed almost entirely of eosinophiles. Of course this fact was seized upon by the allergists, and it is very much the basis of the allergic theory of the disease.

The Early Skeletal Changes in Gargoylism. Dr. John Caffey, New York.

Three patients, one a premature infant, were observed in early infancy; all showed a generalized severe demineralization of the skeleton which suggested adrenal rickets or hyperparathyroidism. Chemical studies of blood and renal function all gave normal results. With increasing age the characteristic skeletal basis of gargoylism evolved from the earlier demineralized lesions, and the patients become typical gargoyles clinically. So far as could be determined, the prenatal, neonatal, and earliest infantile aspects of gargoylism have never been observed before.

Prolonged Obstructive Jaundice in Infancy. Dr. David Yi-Yung Hsia (by invitation), Dr. Paul Patterson Jr. (by invitation), Dr. Fred H. Allen Jr (by invitation), Dr. Louis K. Diamond, and Dr. Sydney S. Gellis, Boston.

A study was made of 156 infants admitted with the diagnosis of possible atresia of the bile ducts because of prolonged jaundice of an obstructive type. In 94 cases the diagnosis of biliary atresia was confirmed by surgical exploration. Operative repair of the defect could be attempted in only 22 of the infants, and only 4 of them are alive and well.

It was found that obstructive jaundice was the result of inspissated bile due to erythroblastosis fetalis in 23 infants, most of whom had not received exchange transfusions. The criteria for diagnosis of this syndrome and the serum bilirubin levels during the onset were studied. All the infants with this condition made uneventful recoveries.

Thirty cases were due to inspissated bile of unknown cause. A close relationship of prematurity and severe illness in the first few days of life to the onset of this condition is suggested by the data. Although most of the infants with inspissated bile recovered completely, six of them are dead and cirrhosis developed in the other two.

Nine cases were due to miscellaneous causes, including infectious hepatitis in four.

The use of blood grouping and liver function tests in the differental diagnosis of these conditions was studied.

DISCUSSION

Dr. A. Ashley Weech, Cincinnati: I wonder whether Dr. Hsia, with his extensive experience, can give us information on the possible diagnostic significance of the dark green pigment of normal meconium. Although we do not know the nature of the pigment, we believe it gets into the intestine by way of the biliary system. Within recent years I have encountered three cases of congenital atresia of the duodenum below the opening of the ampulla. In two of these the first meconium was devoid of the green pigment. In the third case, in which pigment was present, an alert pathologist was able to demonstrate an accessory common duct entering the intestine below the point of atresia. If the belief is correct that the pigment enters the intestine via the biliary system, then knowledge of the presence or absence of pigment in meconium should afford a simple means of distinguishing between biliary obstruction arising from anomalous development and that appearing subsequent to birth from inspissated bile.

Dr. Joseph Stokes Jr., Philadelphia: This is a large and very interesting series. I think Dr. Hsia and his colleagues are to be congratulated on its review. Our group has been particularly interested also in the danger of operating early in such cases. It seems far better to leave them alone. I should be interested in knowing how Dr. Hsia and his group feel about the indications for biopsy.

We have found, too, as I believe they probably have found—although I was not sure from what they said—that flocculation tests are not particularly helpful in such cases.

Dr. Wolman of our group reported last year on a case of serum hepatitis transmitted apparently through the placenta (the baby, delivered by Caesarian section, had no contact with the birth canal and was not fed at the breast) in which the infant's and the mother's blood were shown to be infective, the mother having given no history of jaundice. Two years and eleven months later the mother's blood was again taken. It produced hepatitis with jaundice in two out of five volunteers and hepatitis without jaundice in one volunteer. In all the incubation period was long. Jaundice had occurred in the infant about two months after birth. This obviously is a possible method of transmission of the disease and may help to clarify the epidemiology.

I believe that some of the cases of Dr. Hsia and his group may well be viral hepatitis, because in several instances in which we carried out biopsies the results apparently indicated that viral hepatitis was present.

These patients are particularly bad risks for surgery. There seems to be every reason, as Dr. Hsia has mentioned, why they should be left until a possible mucus plug has disappeared. One of the most interesting points about the possible epidemiology of a few cases is that in about seven instances in which individuals have been shown to be carriers of the serum hepatitis virus, none of them has had a history of jaundice. Thus there may be a good many mothers without a history of jaundice who give birth to infants who have the virus in the blood stream. The disease could possibly be venereally transmitted. It may be transmitted, of course, through the spermatozoa as well as directly through the placenta.

Dr. McGovern, New York: Dr. Stokes brought up the point, as many of us have, that perhaps these children would be better off left alone for a while. Dr. Hsia has referred to a waiting period.

My group became particularly interested in this problem almost two years ago, when two infants admitted to the New York Hospital with definite signs of obstructive jaundice were operated on and, although nothing abnormal had been found by x-ray of the hepatic ducts, died during the postoperative course.

We then made a survey similar to that of Dr. Hsia and his group, on a smaller number of infants, at the New York Hospital. We are delighted that many of the findings are similar. We had a series of 30 infants; 17 showed congenital anomalies, of which 13 were of the group called inspissated bile. It is interesting that in following up all these cases, of which the longest began 10 years ago, and the shortest 6 months ago, we found that of the 17 patients with congenital anomalies 1 is well today and 1 has cerebral palsy.

Of the 13 infants with inspissated bile, we operated on 4. All died during the postoperative period. The other nine children did not go to surgery for various reasons. One particular reason I remember well: The mother signed the child out against advice. But the significant finding was that these nine children are well today. We checked on them in October and November of last year.

Dr. Hsia refers to the waiting period. In December we suggested a waiting period of at least two months because we had had no laboratory evidence of liver damage and we had had no evidence of portal hypertension in any of the infants up to that time. We realize that perhaps we should wait a good deal longer in many cases.

The incidence of prematurity to which Dr. Hsia referred was even greater in our group. Of the 13 infants with inspissated bile, 10 were originally of premature weight.

We also looked for other possible etiological factors. Thanks to Dr. Stokes, we were able to carry out some of the infectious hepatitis skin tests. We called in the living infants and the mothers of the second group and gave each individual a skin test. All of the results were negative.

Dr. Sydney S. Gellis, Boston: The observation that led to this study was that some children believed to have atresia of the bile ducts, whose condition on exploration was declared inoperable, were sent home to die but became well.

I want to discuss briefly the role of liver biopsy in such cases. As has been pointed out, a number of cases of the inspissated bile group of unknown cause may well be due to hepatitis. We feel definitely that there is no need in the majority of these cases of doing liver biopsy since there is no specific treatment at the present time for hepatitis. On the basis of our data surgical exploration for the purpose of examining the biliary tree and obtaining a liver biopsy specimen appears to increase the mortality rate. Punch biopsy would probably yield helpful information, but I feel that it, too, is a potentially hazardous procedure.

I feel, personally, that a waiting period of two months may not be necessary. I think that if enough determinations have been done to make absolutely certain that no bile is coming through, no urobilinogen is appearing in the urine, and the bilirubin trend is generally upward, surgical exploration may be carried out.

The chance of getting a bilitary atresia successfully anastomosed is obviously exceedingly small; hence delay in surgery appears entirely justified.

DR. DAVID YI-YUNG HSIA, Boston: I want to thank the various discussers. I am sorry I cannot answer Dr. Weech's question; we had poor data on the color of the pigment of the first meconium stool, since the children were all referred to the Children's Hospital from other hospitals.

However, we have been impressed by the fact that a number of babies with true biliary atresia do have colored stools—stools which are sometimes green, sometimes gray, and sometimes brown—and that bile studies of the stool using the Harrison spot test have been consistently negative. In 67 cases of biliary atresia in which Harrison spot tests were done the results were negative.

To answer Dr. Stokes, I agree with him that flocculation tests for infectious hepatitis in infants under 6 months of age are extremely unreliable. That has been our experience and also the experience of the great Ormond group in England. Occasionally we have seen a baby in this age group with a positive flocculation test who did have infectious hepatitis, but in general the test cannot be relied upon.

We should very much like to try out in this age group the skin tests which Dr. Stokes and Dr. Drake have been perfecting. I am sure that a certain number of infants get infectious hepatitis from the mother, whether or not the mother has any signs and symptoms of it. The fact that some babies become jaundiced within four weeks or less after birth would certainly suggest that the hepatitis is transmitted from the mother rather than acquired.

Just out of interest, we followed up, some 6 to 10 years later, the infants born of a group of 15 mothers with noninfectious hepatitis. All of them were living and well, having had no evidence of hepatitis or similar illness during infancy. This observation does not rule out the possibility that in occasional instances infectious hepatitis can be transmitted from the mother to the child. Although we have not yet been able to find a case such as that described by Dr. Stokes, I am sure that sooner or later we shall.

I want to thank Dr. McGovern and Dr. Weech for their remarks. We became especially interested in this problem primarily because of experiences in the New York Hospital, and I am happy to find that their figures and ours are in general agreement.

Hemolysis in Hydrogen Peroxide of Erythrocytes of Premature Infants: Effect of Alpha Tocopherol. DR. HARRY H. GORDON, Baltimore, and (by invitation) J. P. DE METRY and G. CSAPO, Denver.

Gyorgy and Rose have shown that the erythrocytes of rats fed a diet deficient in alpha tocopherol can be hemolyzed by hydrogen peroxide before symptoms of deficiency appear. The susceptibility to hydrogen peroxide of the red blood cells of 35 premature infants and 25 adults was determined according to a slight modification of their method. All 25 adults showed hemolysis in hydrogen peroxide which was less than 10% of that in distilled water.

In 39 observations on premature infants more than 10 days old who had been fed partially skimmed milk mixtures, 30 (77%) showed over 50% hemolysis and only 2 (5%) showed less than 10% hemolysis. Of four observations on premature infants in the same age group fed an evaporated milk mixture, three showed over 50% and one 22% hemolysis. Of 17 observations on infants less than 10 days of age, only 4 (24%) showed over 50% hemolysis and 9 (53%) showed less than 10% hemolysis. Serial observations on individual infants confirmed this trend to development of a positive hemolysis test with increasing age and therefore duration of the diet.

Susceptibility to hydrogen peroxide persisted as long as the infants were observed without tocopherol supplementation of their diets. In each of 13 trials on 11 infants the in vitro hemolysis was reversed by feeding alpha tocopherol. The smallest amount added to the diet was only approximately 1 mg. of alpha tocopherol acetate and this was effective in each of the two infants to whom it was given. These data confirm the suggestions of Owens and Owens and of Wright, Filer, and Mason based on their studies of serum tocopherol, and the milk analyses of

Quaife and Harris, that customary cows' milk feeding of premature infants may require supplementation with alpha tocopherol. They suggest further study of infants with scleredema for whom vitamin E therapy has been recommended by Gerloczy and others.

The in vitro hemolysis in hydrogen peroxide was less than 10% in single determinations on each of three children with leukemia, one with acquired hemolytic anemia, one with spontaneous hypoglycemia, one 18-month infant with pellagra and tuberculosis, and one 7-week infant with cerebral agenesis and retarded physical development. Cord blood of an infant with isoimmunization who developed kernicterus and a sample from a 12-hour-old infant with only serological evidence of isoimmunization showed 18% and 37% hemolysis, respectively, within the range for normal newborn full-term infants.

DISCUSSION

DR. PAUL GYORGY, Philadelphia: I wish to thank Dr. Gordon for his gracious remarks. It is especially gratifying that a method of one laboratory not only worked but worked better in another laboratory.

The hemolysis test has one advantage over the total vitamin E measurement of the serum because it measures free active vitamin E. Part of the vitamin E is bound in the serum on protein, and only that part which is free acts, apparently, on the erythrocytes.

Last year I suggested that perhaps the erythroblastosis seen in the newborn infants of diabetic and prediabetic mothers has a relation to the phenomenon indicating increased turnover of the red blood cells.

I also suggested that perhaps liver injury, which is part, at least in experimental animals, of the vitamin E deficiency, and massive pulmonary hemorrhage, which is perhaps the most specific manifestation of the vitamin E deficiency, may be prevented in Rh incompatibility by giving vitamin E to the mother to prevent the vitamin E deficiency of the newborn.

In animals, one can give vitamin E to the pregnant mother to prevent vitamin E deficiency in the newborn. Last year, however, in studies in which up to 500 mg. daily of vitamin E was given to human mothers, only statistically insignificant changes in the new hemolysis test with hydrogen peroxide were observed. Apparently the transplacental transport of vitamin E in human beings is exceedingly difficult, if possible at all—a very interesting observation.

I should like to ask Dr. Gordon two questions: first, whether he thinks that the anemia of premature infants, which is an important practical problem, may be related to the vitamin E deficiencies seen in premature infants and, second, whether he has observations on newborn infants with manifest Rh incompatibility.

DR. CARL H. SMITH, New York: Many years ago I tested the capacity of the red cells of infants and children of different ages for adsorbing dilute solutions of methylene blue. The test consisted of thoroughly admixing measured amounts of dilute methylene blue solution with blood from the heel or finger and exposing the mixtures to ice-box temperature. The degree of adsorption by the red cells could be correlated with the depth of the color remaining in the overlying column of fluid after the red cells settled out. Appropriate studies showed unequivocally that the red blood cells constituted the elements of the blood responsible for the decolorization and that the dye was removed from the solution by the process of adsorption. It was further shown that the adsorbed methylene blue was attached to the stroma of the red blood cells.

It was noted that under physiological conditions the blood of the young infant during the first four months of life possessed the unique property of decolorizing the solution of dye more rapidly and more intensively than the blood of older infants and children. It was also suggested that the extensive surface presented by the total mass of red blood cells in the circulation might account for the adsorption of a diversity of substances dissolved or suspended in the plasma, such as metabolic, immune, or endocrine products.

Since the publication of these studies a number of investigations have been reported supporting this thesis, notably the adsorption of influenza hemagglutinins on chicken red blood cells and of Rh antibody by human red cells. On this basis it is possible that the reversal of hemolysis in infants fed alpha tocopherol might be explained by its initial adsorption on the surface of erythrocytes. The subject for further investigation, it seems to me, is whether the ingestion of alpha tocopherol alters the surface of the red cell after its adsorption from

the plasma or whether resistance to hemolysis by dilute hydrogen peroxide results from structural changes within the red cell effected in the bone marrow. It may be possible to investigate this point by elution experiments and later exposure to the hemolytic agent. If it is found that suplementation of diets with tocopherol results in a structural change, this discovery becomes a matter of great importance. In the anemias, for instance, the alteration of the red cells rendering them less destructible is an extremely desirable objective in therapy. In any event, the problem is to determine whether tocopherol operates at the bone marrow level or whether it is adsorbed passively by the unaltered red cells in the peripheral blood.

DR. SAMUEL Z. LEVINE, New York: Dr. Gordon is to be commended on his continued pioneering work in the nutrition of premature infants. This application of a technique to human biology with respect to a vitamin about which we know little or nothing, and its application to the nutrition of premature infants, opens up a wide field.

Dr. Gordon mentioned that adults did not show positive reactions to the hemolysis test. I wonder whether he did any determinations on normal full-term infants and whether he determined alpha tocopherol levels in the blood and correlated the levels with the percentage of hemolysis in individual premature infants.

DR. EUGENE KAPLAN, Detroit: Stimulated by Dr. Gyorgy's alloxan hemolysis in rats several years ago, my colleagues and I attempted empirically, without the advantage of serum tocopherol levels, to investigate the suplementation of the diet of children having intrinsic erythrocyte disorders with hemolysis, giving them 200 to 500 mg. of tocopherol a day. In a case of severe hemolytic anemia associated with congenital porphyria, treatment extended three or four months. We were unable to influence the course of the disease, on the one hand, or the urobilin excretion, on the other.

DR. HARRY H. GORDON, Baltimore: We have performed the hydrogen peroxide hemolysis test for two infants with isoimmunization. Cord blood was taken from one infant who subsequently died of kernicterus; the second infant showed only serological evidence of isoimmunization. Hemolysis was 18% for one infant and 37% for the other. We have found, on occasion, higher levels of hemolysis, as has Dr. Gyorgy, in normal full-term infants at birth.

Wo do not know whether in vivo hemolysis takes place spontaneously in premature infants under the dietary conditions described. If it occurs it may be one factor contributing to the anemia of prematurity.

Dr. Carl Smith's point about methylene blue is of interest because Christensen and Dam have shown that methylene blue decreases the susceptibility of the red cells of vitamin E-deficient rats to dialuric acid. This observation suggests that the protective action of tocopherol may be a function of its antioxidant properties. Incidentally, Dr. Smith, Dr. Gyorgy found that after incubating red blood cells from vitamin E-deficient rats with tocopherol, he could wash the cells and still find them protected against the hemolyzing agent.

We have made no determinations of plasma tocopherol in our infants. We are more interested in the concentration in the red cells; also, I believe that micromethods are not available for such determinations.

Fragility of Erythrocytes Exposed to Rh Antibodies in Vivo and in Vitro. DR. ALFRED M. BONGIOVANNI (by invitation), and DR. NEVA M. ABELSON (by invitation), Philadelphia.

The fragility of erythrocytes in normal newborn infants and infants with erythroblastosis fetalis was determined by mechanical methods (of Castle) and special photometric osmotic methods. The red cells of infants were found to be more resistant than those of adults, so that adequate controls were first established.

The erythrocytes of infants with erythroblastosis fetalis showed a significantly greater osmotic fragility than normal in glycerol and 0.36% saline, but not in thiourea or 0.4% saline. The mechanical fragility was greatly increased in all diseased infants. However, no correlation with the severity of disease or the degree of maternal sensitization was noted.

It was not possible to increase the fragility of red cells from normal infants by incubation with various sera from sensitized adults or diseased infants. This observation suggests that

factors other than the Rh antibodies produce the alterations in fragility noted in diseased infants. To date, the use of adult serum, Coombs serum, placental extracts, and other substances, in addition to Rh antibodies, has been without significant effect.

DISCUSSION

DR. CARL H. SMITH, New York: I wish to congratulate Dr. Bongiovanni on his fundamental contribution in this rapidly developing field. I should like to ask him whether he has been able to correlate quantitatively the presence of spherocytes in the peripheral blood with alterations in fragility. In other words, is there any relationship between what is observed microscopically and the results he has demonstrated on the slides?

DR. FRED H. ALLEN JR., Boston: I should like to speak for Dr. Diamond and myself, as well as the rest of our group in Boston, in expressing our admiration for the very valuable contribution to our understanding of the basic physiopathic mechanisms in erythroblastosis fetalis, which we still understand poorly.

DR. DAVID YI-YUNG HSIA, Boston: I should like to make one brief comment on Dr. Smith's question. My group has, during the last few months, had occasion to do both osmotic and mechanical fragility studies with and without incubation on a small number of babies with ABO erythroblastosis. As you know, the Johns Hopkins group has reported increased fragilities determined osmotically in such infants.

Our experience with osmotic fragility studies, both with and without incubation, has not been particularly striking. In mechanical fragility studies, without incubation, the results were within normal limits for newborn babies.

In the incubation fragility test as described by Fenn and Castle we were able to demonstrate marked hemolysis in infants with ABO erythroblastosis.

DR. ALFRED M. BONGIOVANNI, Philadelphia: In answer to Dr. Smith, we did not do precise spherocyte counts in the course of our studies. However, smears were prepared of the blood from all patients, and spherocytes were seen in most. We do not know the mechanism of blood cell destruction with the mechanical method of determining erythrocyte fragility. We are not sure that there is a relation between the number of spherocytes and increased cell destruction with this method. In fact, in two instances of congenital familial hemolytic anemia with large numbers of spherocytes, the mechanical method revealed fragility little greater than normal, while the osmotic method revealed great differences. The osmotic methods are better understood. In a few instances smears were made during the course of the mechanical stress and an increase in the number of spherocytes was not observed. Some of the cells assumed peculiar forms, with the appearance of pseudopod-like protrusions on their surfaces. In two instances osmotic determinations of red cells were made (on controls and cells exposed to Rh antibodies) after a preliminary mechanical test. The osmotic fragility was moderately increased, but there was no difference between the control and the treated cells. I am sorry that I cannot give more information on this point.

Folic Acid Deficiency: Experimental and Clinical. DR. CHARLES D. MAY and (by invitation) DR. AGNES HAMILTON and DR. CHARLES T. STEWART, Minneapolis.

It is important to determine the circumstances which may lead to a deficiency of folic acid in infants. One definite manifestation of folic acid deficiency is found in the marrow as a megaloblastic type of blood formation. Normal infants reared on the usual feeding regimens have seldom been found to become deficient in folic acid. Deficiency of folic acid in infancy almost always develops because of pathological circumstances involving the infants. The most frequent pathological conditions which have been associated with megaloblastosis are scurvy and infection.

Previously reported experiments demonstrated that folic acid deficiency developed fairly regularly in scurvy. One of our objectives was to conduct experiments concerning the manner in which deficiency of folic acid develops during scurvy. We made a systematic exploration of the effect of ascorbic acid deficiency on the known phases of folic acid metabolism. We studied the absorption of naturally occurring conjugates of folic acid, the synthesis of conjugated folic acid by the intestinal bacteria, the elimination of the folic acid from these conjugates, and the conversion of folic acid to folinic acid.

Another objective was to consider the development of megaloblastosis in infants in spite of an adequate intake of ascorbic acid. If megaloblastosis appears after infection and the ascorbic acid intake has been optimal, treatment with ascorbic acid will have no effect. When megaloblastosis develops as a complication of scurvy, either folic acid or ascorbic acid will be equally effective in restoring the marrow to a normoblastic type. To explore the role of infection in the pathogenesis of megaloblastosis, monkeys reared on cows' milk supplemented with a liberal amount of ascorbic acid were given a series of intramuscular injections of turpentine to produce sterile abscesses. A few such injections caused no megaloblastosis in the marrow, but when injections were continued longer the animals ultimately had typical megaloblastosis. Treatment with ascorbic acid and vitamin B_{12} had no effect on the marrow, but folic acid caused prompt elimination of megaloblasts from the marrow. In untreated animals with megaloblastosis normal amounts of ascorbic acid were found in the liver and adrenals. Microbioassay of the liver of untreated animals revealed that a deficiency of folic acid was induced by the turpentine injections.

Experiments as to the relation of "stress" to depletion of body stores of folic acid were carried out. Tissue analyses for ascorbic acid, the folic acid group, and vitamin B_{12} were done. An infant with megaloblastosis in association with infection, without ascorbic acid deficiency, was observed.

The data obtained permit a hypothesis as to the pathogenesis of megaloblastosis in infants who have recurrent infections but are adequately supplied with ascorbic acid. The relationship to the type of megaloblastosis complicating scurvy was considered, as well as treatment of sick infants.

DISCUSSION

DR. WOLF W. ZUELZER, Detroit: This is a beautiful piece of work and brings us significantly closer to the solution of the mystery which still surrounds the pathogenesis of megaloblastic anemia in infancy.

Three or four years ago, at the regional meeting of the American Academy of Pediatrics in Buffalo, I presented a working hypothesis which seems to be borne out by the work of Dr. May and his associates. The assumption of my group was that in certain conditions, among them infections, diarrheal disease, and scurvy, the requirements for the essential hemopoietic factor, presumably folic acid, are increased above normal and are not met by ordinary, let alone suboptimal, intake of pteroylglutamic (folic) acid. It was shown in our laboratory that megaloblastic anemia developing in these conditions can be prevented and corrected with additional doses of pure PGA even in infants with manifest uncorrected scurvy.

Our clinical experience has been in agreement with the evidence presented by Dr. May and his co-workers. Response to vitamin B_{12}, vitamin C, or a combination of these two substances is inconsistent. These vitamins have failed in the majority of our cases. On the other hand, the administration of folic acid and, in a more limited experience, of citrovorum factor has been invariably successful. There is now excellent evidence that the deficiency in megaloblastic anemia of infancy in the overwhelming majority if not all cases is actually one of folic acid or closely related substances. Dr. May's work bears out this observation experimentally and also confirms the clinical impression that a multiplicity of factors can produce relative deficiency and that perhaps an entirely nonspecific factor such as stress is the common denominator which induces the specific defect in nucleic acid metabolism.

As you all know, megaloblastic anemia as a clinical syndrome has become rare in the last few years, and this fact might throw some doubt on the hypothesis presented, since the disappearance coincided with the introduction of excess ascorbic acid into diets on which many infants formerly acquired both megaloblastic anemia and scurvy. Undoubtedly the reduction in the incidence of ascorbic acid deficiency has a bearing on the incidence of megaloblastic anemia. It is worth pointing out, however, that as a subclinical condition the entity is far more common than most of us realize. In recent years my colleagues and I have performed bone marrow aspirations on many infants who were ill with prolonged diarrhea whose diet during their illness was one of semistarvation but who had received the usual supplements of vitamin C and of the vitamin B group but not of folic acid or vitamin B_{12}. A significant number of such children were found to have incipient but clear-cut megaloblastosis in the bone marrow as the sole indicator of the

deficiency state. We can say therefore that the symptomatic state is not nearly as common as is indicated by the more sensitive method of bone marrow aspiration, which detects the marginal deficiency.

DR. HAROLD E. HARRISON, Baltimore: Dr. May has so nicely related folic acid and vitamin C that I am made bold to ask him a question which may be putting him to a more severe test. What is the mechanism involved in the relationship between folic acid and vitamin B_{12}?

I have observed a baby with megaloblastosis who apparently had a congenital deficiency of absorption of vitamin B_{12}. This child had a characteristic picture of megaloblastic anemia but responded not at all to folic acid, even in extremely large doses or in doses given intramuscularly, but did respond in typical fashion to vitamin B_{12} given intramuscularly and to very large doses given orally. The child had a relapse every time administration of vitamin B_{12} was stopped. Perhaps Dr. May could help us in commenting on the interrelationship between folic acid, folinic acid, and vitamin B_{12}.

Effects of Withholding Fluid Intake in the Immediately Postnatal Period. DR. JOHN D. L. HANSEN (by invitation), and DR. CLEMENT A. SMITH, Boston.

During the immediately postnatal period, the infant is expected to make numerous physiological readjustments while in negative water balance. Clinical observations have suggested that neonatal renal function is adequate for these purposes, and it has been proposed that any renal inadequacy of premature infants might be counterbalanced by the availability of excess body water for urine formation. These assumptions are under laboratory investigation. To date, sodium, chlorine, potassium, and nitrogen balances have been measured and serum chemistry studies made on 6 infants allowed no water for three days after birth and on nine controls given approximately 50 cc. of water per kilogram a day. On the fourth day infants of both groups were given 100 cc. per kilogram of 5% glucose in water, and milk feedings were then begun. The two groups (referred to as thirsting and fasting infants) were comparable in range of gestational age from term infants to premature infants of 34 weeks. Convenient comparisons with normal adults were obtained from the life-raft ration studies of Gamble, Butler, and their co-workers.

The most striking differences (per kilogram of body weight) brought about in all infants by thirsting as opposed to fasting were the expected increases in body weight loss and calculated body water loss, and the reduction of urine volume. On the other hand, the urine outputs of sodium and chlorine were almost exactly the same under thirsting and fasting conditions. Thirsting was accompanied by moderate alterations in urine outputs of potassium and nitrogen without a consistent trend.

The serum concentrations of sodium and chlorine rose by averages of 12 and 7 mM. per liter respectively and that of blood urea nitrogen by 9 mg. per 100 cc. at the end of the three days of thirsting. The comparable figures for the fasting infants were reductions of 4 and 3.5 mM. per liter in sodium and chlorine and of 3 mg. per 100 cc. in blood urea nitrogen.

Comparison of these findings in infants with those for adults shows the following outstanding differences:

Weight loss is relatively less in adults than in infants, whether fasting (3.2% in adults, 8.3% in infants) or thirsting (6% in adults, 13.5% in infants), and calculated body water loss proportionately less under both conditions. The urine volumes of thirsting adults also are lower than those of thirsting infants. There are distinct increases of sodium and chlorine outputs in thirsting adults whereas—as stated before—there was practically no change in those of infants. This observation implies some inability on the part of infants to increase excretion of extracellular electrolytes under thirsting conditions. Adults were able to achieve a urine solute concentration of 1.5 osmole per liter (infants, maximum 0.68), and, according to serum chemistry studies, to maintain unchanged extracellular electrolyte concentration.

The most premature infants differed from the mature ones, whether thirsting or fasting, by moderately greater body water losses but very much higher excretions of sodium, potassium, and chlorine in urines of greater volume. Urine osmolarity achieved during thirsting was similar at all gestational ages, which presumably prevented serum concentrations of the most premature from rising higher than the average for thirsting infants.

On the fourth day (when all infants had a similar fluid intake) infants who had thirsted gained weight by an average of 3% and showed return of serum concentrations to more nearly normal levels. Those that had fasted remained unchanged in weight and in serum chemistry. During the three-day thirsting period no infant had fever or other clinical evidence of gross disturbance.

Premature infants showed in this study neither superior nor inferior adjustment to the three-day withholding of fluid as compared with full-term infants. All of the infants appeared to adjust less successfully than adults to the experimental circumstances.

DISCUSSION

DR. HENRY L. BARNETT, New York: It is a little difficult for me to discuss this paper without presenting the one that I am going to give. I should like to point out, however, certain things about this interesting study of a practical problem. Despite the many indications of functional immaturity of the kidney in the premature infant, here again we have a demonstration that it does its job well.

I think one other problem appears in these data which cannot be answered at the present time. This problem concerns the standard of reference to be used in comparing the small infant with the adult. It was clear from Dr. Hansen's slides that if one calculates water loss during thirsting on a per kilogram basis, the results are essentially opposite to those obtained if a per square meter basis is used.

One further point that I should like to make is that despite the fact that these observations were set up along the pattern of those made by Dr. Gamble, Dr. Butler, and others on fasting adults, many uncontrollable differences between the infant and the adult remain. As Dr. Hansen indicated, these differences need to be considered in comparing figures for infants and adults.

DR. HAROLD E. HARRISON, Baltimore: I should like to ask Dr. Hansen whether he thinks the rise of serum sodium concentration shown by the thirsting infants is of clinical significance. If so, it would of course increase the emphasis on giving adequate amounts of water during the first four days. Obviously, the thirsting babies did show a disturbance of the osmolar concentration of the extracellular fluid.

DR. HARRY H. GORDON, Baltimore: I should like to ask Dr. Hansen whether he has any data on serum electrolyte concentrations after the third day, particularly in relationship to either dilute or concentrated feedings.

DR. NATHAN B. TALBOT, Boston: I should like to ask the authors whether they have performed any studies on these infants which suggest that they lose electrolytes in the latter half of the first week of life.

DR. S. A. KAPLAN, Cincinnati: One of the fascinating points of this study is the equality of electrolyte excretion which is produced in hydrated and nonhydrated infants. Wednesday morning, Dr. C. D. West presented a paper to the Society for Pediatric Research in which he showed that the electrolyte loss in the urine is independent of the state of hydration of the body. It is gratifying to see so soon a clinical application of this study in which the results of the group at Cincinnati have been confirmed.

One wants to emphasize the fact that when water was administered under the conditions of the present study and under the conditions of the experiments reported by Dr. West, there was no effect whatsoever within the limitations of the figures presented on the slides on the sodium chloride and potassium losses in the urine.

DR. CLEMENT A. SMITH, Boston: Dr. Hansen's comment that the baby might be born with enough water in his body to cover all his excretory needs for three days, and, if premature, to cover these needs even longer, was originally my own rather loose thinking. I think we have shown that although babies can tolerate absence of intake (and we have shown it on many more babies observed clinically), distortions of serum chemistry to take place. I do not think they are serious, particularly in view of the divergence from the adult normal standard in all homeostatic phenomena shown by newborn, and particularly premature, infants.

We hoped during our study to find an infant as markedly edematous as those we sometimes see, but all of the edematous babies were girls or were otherwise unsuitable for our investi-

gations. Of twins who were moderately edematous at birth, one was in the thirsting group and the other received water. In these twins, the provision of water did not seem to shorten the four- or five-day interval during which the edema disappeared.

Dr. John D. L. Hansen, Boston: I should like to thank the speakers for their comments. I think Dr. Smith has partly replied to Dr. Harrison's question. We do not really know the clinical significance of the raised serum sodium, but clinically the babies appear to be perfectly well.

In answer to Dr. Gordon, the serum concentrations on the fourth day—that is, after the infants had all received their glucose—tended to return to normal. We have no figures on the electrolyte levels after the four days.

As to Dr. Talbot's question about electrolyte outputs later in the week, we have no data on that. All I can say is that on the fourth day, when all the babies got water and glucose, those who had been thirsting did not put out more electrolytes than those who had been fasting.

Homeostatic Boundaries to Safe Parenteral Fluid Therapy. Dr. N. B. Talbot, Dr. J. D. Crawford (by invitation), and Dr. A. M. Butler, Boston.

This paper is based on observations concerning the limits of capacity of the organism to conserve or to excrete according to need water and certain solutes (especially sodium, potassium, and phosphate). Particular attention was given to the effects of varying the inorganic solute content of fluids infused parenterally upon bodily capacity to sustain water concentration homeostasis under conditions of health and illness. It was shown with the aid of diagrams that the administration of 5 or 10% dextrose solution at a rate of more than about 120 cc. per square meter an hour (3 liters per square meter a day) makes the patient liable to water intoxication. Contrariwise, it was shown that, while 0.85 gm. per 100 cc. of saline in dextrose solution, which has 300 milliosmoles of inorganic solutes per liter, cannot cause water intoxication, it is likely to lead to excess sodium retention, edema formation, and cellular potassium deficiency. At the same time "physiologic" saline failed to provide enough free water to meet minimum body needs for insensible, stool, and urine water expenditures. It was suggested that the difficulties inherent in the use of the first two types of solution are minimized when patients are given fluids containing in addition to dextrose a total of about 150 milliosmoles per liter of a suitable mixture of electrolytes at a rate of between 2 and 3.5 liters per square meter in 24 hours. We concluded that it is greatly to the advantage of patients with functionally adequate renal-endocrine homeostatic symptoms to be given fluids of this type, for it would appear that these automatic systems usually are better able to make adjustments exactly suited to the patient's needs than are we as physicians with the limited information ordinarily available to us.

DISCUSSION

Dr. Clement A. Smith, Boston: First, I should like to congratulate Dr. Talbot for putting on three slides the greatest amount of understandable information I have ever seen in so small a space. Second, would he, from clinical or other experience, include newborn or premature infants among the patients covered by his rules on the applicability of solutions? From our experience his solution might be a little high in electrolytes for premature and full-term newborn infants. Is it quite safe for these patients?

Dr. Robert Cooke, New Haven, Conn.: I think the authors are to be commended on making fluid therapy so simple. However, it would seem to me that a slightly more logical analysis of the problem of fluid therapy might be more advantageous, if not for the patient, at least for the teaching of fluid therapy.

It would seem to me that in fluid therapy there are distinct requirements. There are requirements of materials for the usual supply of chemicals to the patient under ordinary circumstances, and those were adequately discussed. They are covered by the materials Dr. Talbot mentioned.

However, in the usual case of fluid therapy there are other problems, such as the presence of a deficit before the beginning of therapy. Dr. Talbot has suggested that his solutions might be used under almost all circumstances. It is easy to visualize many clinical circumstances under which they would not be optimal solutions, and one would not have to have a great deal of laboratory or clinical information to use solutions which might be considerably better for the replacement of deficits.

In addition to the usual losses of materials from the body, there are abnormal losses which must be replaced in about the same quantity and in the same kind. For their replacement I should think that the use of these solutions would be a long way from the best procedure. Without too much difficulty, I should think, the house staff or other physicians might be able to supply somewhat better materials.

DR. GRACE M. GUEST, Cincinnati: I should like to echo the recommendations just expressed for caution in the use of so-called "all-purpose" solutions in parenteral fluid therapy. The needs for replacement of different elements in the body and the ability of the body to assimilate them in states of acidosis, dehydration, and recovery may vary considerably during different stages of the crisis. At such times gross changes in metabolic pathways as well as in electrolyte structure of body fluids and cells may influence the choice of therapy. A number of investigators have pointed out that the administration of potassium may be dangerous in the presence of hyperpotassemia, often present in conditions of severe acidosis and dehydration when cellular catabolism leads to rapid liberation of intracellular elements. Cellular catabolism is aggravated by the state of acidosis. Later, when acidosis is corrected and pH of the body fluids is brought to normal, restored anabolic processes lead to an avid uptake of potassium and phosphorus and other intracellular elements by the cells from extracellular fluids; at that time even huge quantities of potassium and phosphate solution may be given with impunity—and benefit. In the presence of renal impairment, with hyperphosphatemia and hyperpotassemia, there may be grave dangers from the administration of solutions containing potassium and phosphate salts. For these reasons I have adhered to practices of administering fluids in sequence (*e. g.*, in treating diabetic coma), first solutions containing sodium chloride and sodium bicarbonate to improve the circulating blood volume and to correct acidosis, then glucose solution and multielectrolyte solutions, after the restoration of physiologic cellular function is assured.

DR. MITCHELL I. RUBIN, Buffalo: I should like to express another word of caution regarding a standard solution, particularly for administration in the immediate postoperative state in infants. There is some evidence that immediately after operation there is a decrease in capacity to excrete both the water and the salt load. I have seen infants who were given calculated amounts of fluids at that time and have seen, I think, death from edema status.

I wonder whether the authors would comment on the importance of limitation of fluids immediately after operation in a child not seriously dehydrated before operation.

DR. NELSON K. GRIMAY, New Orleans: Dr. Guest and Dr. Rubin have followed Dr. Cooke's general remarks with specific comments, to which I should like to add a question about the use of a solution of this sort in the therapy of alkalosis, such as we see, for instance, in hypertrophic pyloric stenosis. The solution is alkaline. It contains lactate ion, and it also contains phosphate. In both situations, it seems to me that it might precipitate tetany. I have seen tetany occur in the therapy of children with hypertrophic pyloric stenosis and alkalosis with the usual solutions, which do not contain phosphate. It has been my practice not only to use neutral solutions containing potassium in treating severe alkalosis, but to add calcium when the carbon dioxide is over 40 mM. per liter.

DR. ARILD E. HANSEN, Galveston, Tex.: Perhaps it is not fair for a person who is not a "water man" to make comments, but coming from a part of the country where summers are long and hot I wonder whether differences in environment may affect the applicability of a "universal" solution such as the one suggested. More water is consumed but there is excess loss of sodium chloride; hence, it may be necessary to take this factor into consideration.

DR. NATHAN B. TALBOT, Boston: I should like to thank the discussers for emphasizing various important points.

With regard to Dr. Smith's question concerning the applicability of the thesis of our paper to the premature infant, the following may be said: First, McCance and Barnett have shown that the glomerular filtration rate of young infants is roughly half that of children and adults. This observation presumably means that the upper homeostatic limits of tolerance of young infants, including premature ones, for water and electrolytes is proportionately reduced below adult levels.

Dr. Cooke is concerned about the repair of body water and electrolyte deficits. Provision is made for this potential need as well as for such abnormal maintenance requirements as may result

from diarrhea, vomiting, intestinal drainage, or the like by giving the patient water and electrolytes in excess of normal minimum maintenance requirements. At the same time, rates of water and electrolyte administration are kept within the upper limits of physiological tolerance. As a result, the patient is in a position to use the aforementioned excess for repair of deficits if they exist or to excrete the excess quantitatively if there is no bodily need for them.

This automatic rejection of unneeded water and electrolytes depends upon an adequately functioning cardiovascular-endocrine-renal homeostatic mechanism. In patients who are in a state of circulatory collapse, such as the patients in diabetic coma mentioned by Dr. Guest, the capacity of this mechanism to handle successfully such substances as potassium and phosphate may be considerably impaired. Accordingly, we almost always start treatment of such patients by giving half or two-thirds isotonic sodium salt in dextrose solution at a rate of about 8 cc. per square meter per minute for one to two hours until urine flow is reestablished. By this time, and especially if an electrocardiographic tracing shows none of the changes of potassium intoxication, it usually is safe to change over to the aforementioned multiple electrolyte type of therapy.

These comments may be closed by stating that we have attempted to define the physiological limits of tolerance of the ordinary type of patient for certain of the more commonly used constituents of parenteral infusion fluids. It remains to be determined how often it is necessary or advantageous to give water or electrolytes at rates outside these limits.

Regulation of Renal Water Excretion in Premature Infants. Dr. Henry L. Barnett and (by invitation) Dr. Jorgen Vesterdal, Dr. Helen McNamara and Dr. Henry D. Lauson, New York.

It is becoming increasingly clear that greater individualization is required in the treatment of abnormal losses or retention of water and electrolytes in young infants. This concept is based in part on the generally held belief that immaturity of kidney function in very young infants imposes a limitation on their ability both to conserve water during dehydration and to excrete water given in excess. However, the extent of these limitations has not been defined and there is no general agreement concerning the renal mechanisms responsible for them.

The rate of excretion of water by the kidneys is now known to be influenced by the rate of glomerular filtration of water, by activity of the antidiuretic hormone of the posterior pituitary, and by the rate of solute excretion. In the present study, the effects of these factors on renal excretion of water were investigated in premature infants during short periods of water deprivation and after the administration of water and of vasopressin injection (pitressin®).

The results indicate that during water deprivation young premature infants are unable to concentrate urine to the same extent as older infants and adults. However, osmolar concentrations in urine up to 700 milliosmoles per liter demonstrated that the extent of this limitation is less than generally believed. The response of premature infants to vasopressin injection (pitressin®) given intravenously during water diuresis is also less than that of adults, although again the difference is less than previously thought.

Young premature infants respond to administration of water with increases in rate of urine flow and decreases in osmolar concentration which are only slightly less than responses observed in adults. Any limitation which may exist in the ability of premature infants to develop a water diuresis can probably be explained by their low rates of glomerular filtration. It is suggested that the failure of others to observe prompt and marked water diuresis in young infants may have been due to: (1) comparisons being made between adults and infants who were given doses of water equivalent on a weight rather than a surface area basis; (2) diuresis in infants receiving human milk being limited by low rates of solute excretion; and (3) the fact that in premature infants but not in adults painful stimuli lower the rate of urine flow by decreasing the glomerular filtration rate, with no increase in urinary osmolar concentration.

Our results indicate that the minimum quantity of water required by premature infants to excrete 1 milliosmole of urinary solute is greater than that required by adults, but by not more than a factor of two. This difference, therefore, is less than generally thought. On the other hand, the maximum quantity of water which can be excreted per milliosmole is practically the same for both premature infants and adults. These results must ultimately influence the principles underlying the treatment of water and electrolyte disturbances in young premature infants.

In addition to the usual losses of materials from the body, there are abnormal losses which must be replaced in about the same quantity and in the same kind. For their replacement I should think that the use of these solutions would be a long way from the best procedure. Without too much difficulty, I should think, the house staff or other physicians might be able to supply somewhat better materials.

DR. GEORGE M. GUEST, Cincinnati: I should like to echo the recommendations just expressed for caution in the use of so-called "all-purpose" solutions in parenteral fluid therapy. The needs for replacement of different elements in the body and the ability of the body to assimilate them in states of acidosis, dehydration, and recovery may vary considerably during different stages of the crisis. At such times gross changes in metabolic pathways as well as in electrolyte structure of body fluids and cells may influence the choice of therapy. A number of investigators have pointed out that the administration of potassium may be dangerous in the presence of hyperpotassemia, often present in conditions of severe acidosis and dehydration when cellular catabolism leads to rapid liberation of intracellular elements. Cellular catabolism is aggravated by the state of acidosis. Later, when acidosis is corrected and pH of the body fluids is brought to normal, restored anabolic processes lead to an avid uptake of potassium and phosphorus and other intracellular elements by the cells from extracellular fluids; at that time even huge quantities of potassium and phosphate solution may be given with impunity—and benefit. In the presence of renal impairment, with hyperphosphatemia and hyperpotassemia, there may be grave dangers from the administration of solutions containing potassium and phosphate salts. For these reasons I have adhered to practices of administering fluids in sequence (e. g., in treating diabetic coma), first solutions containing sodium chloride and sodium bicarbonate to improve the circulating blood volume and to correct acidosis, then glucose solution and multielectrolyte solutions, after the restoration of physiologic cellular function is assured.

DR. MITCHELL I. RUBIN, Buffalo: I should like to express another word of caution regarding a standard solution, particularly for administration in the immediate postoperative state in infants. There is some evidence that immediately after operation there is a decrease in capacity to excrete both the water and the salt load. I have seen infants who were given calculated amounts of fluids at that time and have seen, I think, death from edema status.

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DISCUSSION

DR. NATHAN B. TALBOT, Boston: I should like to compliment Dr. Barnett for his nice contribution. In addition, I want to ask him a question based on observations on one or two children with diabetes insipidus. I have observed, to my surprise, that such children when first given antidiuretic hormone are seemingly unable to react in terms of complete urine concentration during the first days or weeks of therapy. Sometimes it is six months or a year before they obtain full capacity.

I am wondering whether prematurity in infants may be the physiological equivalent of that pathological condition.

DR. HENRY L. BARNETT, New York: I have not known of this apparent adaptation of response to antidiuretic hormone in children with diabetes insipidus. It is difficult, therefore, for me to relate Dr. Talbot's observation to the response of the premature infant to antidiuretic hormone.

I think one thing that needs to be considered is whether a change has occurred in the diet as a result of treatment of the disease. Changes in the diet leading to changes in the rate of solute excretion would influence the quantitative response to the antidiuretic hormone. I think the low rate of solute excretion may ultimately explain why babies do not respond as well as adults to antidiuretic hormone.

A Hitherto Unrecognized Biochemical Difference Between Human Milk and Cow's Milk. DR. PAUL GYORGY and (by invitation), RICHARD KUHN, PH.D., DR. R. F. NORRIS, C. S. ROSE, PH.D., and F. ZILLIKEN, PH.D., Philadelphia.

A specific mutant of Lactobacillus bifidus (variety Penn) isolated from the feces of a breast-fed infant showed no growth in the usual medium satisfactory for most strains of L. bifidus. It required for its propagation the addition of a specific "growth factor" present in human milk. Cow's milk had only one-fiftieth to one-hundredth the activity of human milk. Human colostrum had the highest average relative activity, being closely followed by rat colostrum and then by human milk, rat's milk, and cow's colostrum (taken on the first day). All the other milks tested, in particular the milk from ruminants, such as sheep and goats, in addition to cow's milk, showed only very low activity. Sow's and mare's milk were slightly more active; guinea pig's milk was inactive. This microbiological growth factor is different from all known vitamins and growth factors. Very slight activity was exhibited by liver compounds and practically none by yeast or meat. Meconium was highly active. Human semen, gastric juice (even in a case of pernicious anemia), saliva, amniotic fluid, and tears were also very active. The growth factor occurs in low and higher molecular form in human milk. In meconium it is present in undialyzable form. Purified blood group substances A and B were highly active. From human milk, crystallized levorotatory active products were obtained containing N-acetyl glucosamine, fucose, and galactose, but no amino acids. N-acetyl glucosamine and N-acetyl galactosamine were only slightly active. Higher activity was exhibited by glucosides of N-acetyl-*d*-glucosamine.

L. bifidus variety Penn contains a specific enzyme which inactivates the microbiological growth factor required by the same strain. The enzymatic inactivation of meconium or purified blood group substance as growth factor was accompanied by the reduction of its serological titer as a specific blood group and by the liberation of dialyzable reducing substances, chiefly acetyl-glucosamine.

The recognition of this specific growth factor in human milk and its relation to the blood group substance may represent a specific link with the whole field of immunological reactions and might lead to a better understanding of the higher resistance of the breast-fed infant.

DISCUSSION

DR. JOSEPH STOKES JR., Philadelphia: This highly important work of Dr. Gyorgy and his colleagues is reminiscent of some of the work in connection with pantothenic acid vitamin B_{12}, and folic acid. In the study of those factors, also, the bacterial growth requirements have been used as a means of identification of the new factor.

It is of particular interest that here, perhaps for the first time, a highly important basic nutritional difference has been demonstrated between breast milk and cow's milk—a difference

which appears to be more than a purely quantitative one. One cannot help but wonder about the protection of animals, particularly calves, by means of colostrum. I should like to ask Dr. Gyorgy if he would be willing to discuss that problem.

DR. MYRON E. WEGMAN, New Orleans: I should like to comment only on the evidence as to the resistance of human infants to infection related to breast milk. It seems to me that two questions arise.

In the first place, such evidence as is at hand pertains more to breast feeding than to breast milk alone. The method of delivery is perhaps more important than the content.

The other question has to do with how one can separate the various other factors associated with the breast-fed infant, such as environment and handling, from those of the artificially fed infant in relation to infection.

DR. CLEMENT SMITH, Boston: Was this factor destroyed or disturbed by the preservation of human milk or by its sterilization?

DR. BENJAMIN KRAMER, Brooklyn: It is interesting to note the demonstration of a biological factor which shows a difference between human milk and cow's milk. Fresh human milk facilitates the absorption of lactose, and the blood sugar curve rises much more rapidly after ingestion of fresh human milk than after cow's milk. Fresh human milk if allowed to age or heated loses this peculiar property.

DR. HARRY A. WAISMAN, Chicago: I think Dr. Gyorgy has made a definite contribution. We are all interested in growth factors, especially since they are known to function as coenzymes in all metabolic reactions.

There are two points that I think need to be elucidated. Some of the materials which Dr. Gyorgy added to his media for bacteria were listed. Since we know that some of them are not readily available to bacteria, I wonder whether this factor might not be in conjugated form, accounting for the higher activity in some of the materials he used.

The other consideration is whether recently identified growth factors might be the growth factor described here. One such factor, formerly called protogen, has been identified chemically as lipoic acid.

I wonder whether Dr. Gyorgy has any information along these lines.

DR. PAUL GYORGY, Philadelphia: First, in answer to Dr. Clement Smith, in all microbiological tests the material is autoclaved automatically, which more or less indicates that this growth factor is heat-stable and can be autoclaved for 15 minutes under 15 pounds of pressure. It is stable in liquid form or in frozen form. No deterioration has been found after months of preservation in milk.

The question of breast feeding was not touched upon by me. I do not think that I even mentioned breast feeding. I was talking of breast milk, or human milk. I am not willing, and I know the chairman concurs with me, to go into the highly controversial psychology of breast feeding.

The question of the exogenous need for the substance, raised by Dr. May, is difficult to answer. I have not yet found breast milk devoid of this growth factor. Although I obtained milk specimens from Jamaica from mothers who were obviously in a poor nutritional state, the substance was contained in the milk.

I have not yet found saliva, tested in hundreds of persons, which did not contain the substance. However, the range in saliva is very wide, fluctuating in various persons from 1 to 100.

Being a physician, and very teleologically minded, when I see that this substance is present in very high concentration in colostrum, and then slowly goes down in milk, and when I see that it is present in meconium in very high concentration, I somehow have the feeling that the infant probably needs it.

The calf needs it too, apparently, because—to answer Dr. Stoke's question—cow's colostrum is rich in this factor, in contrast to cow's milk, which is practically free from it. I have the strong belief that the nutritional importance of cow's colostrum may be linked, at least in part, to this factor.

With regard to the question of protein supplements, which also has been raised, I have tested several protein-containing substances which did not interfere with the growth factor in the microbiological test.

Obviously the factor may occur in natural products in conjugated forms. For instance, in meconium it is not dialyzable, whereas in breast milk it is mostly dialyzable. In meconium it must be in conjugated form, perhaps as the polymer of so-called "repeating units." The interesting part of it is that our particular L. bifidus strain which requires this repeating unit, the growth factor, and which must use it definitely in the dialyzable form, not being able to use such a large molecule splits the growth factor off and then somehow also destroys it. The enzyme mixture as extracted from our strain inactivates the growth factor in a specific manner.

Liver concentrates have been found practically inactive. Lipoic acid was completely inactive.

Dr. Kramer's question was answered, of course, by the answer I gave to Dr. Smith, that the milk factor is stable and can be preserved for a long time.

All discussers are to be thanked for their comments.

Utilization of Nitrogen in the Absence of Adequate Calories. Dr. Rudolph C. Ellingson (by invitation), Dr. Arthur J. Mueller (by invitation), and Dr. Warren M. Cox Jr. (by invitation).

As a consequence of the fact that nitrogen utilization is improved by an increased intake of calories, it has been held that the caloric requirement has priority over the nitrogen requirement and that a deficit of calories leads to the catabolism of exogenous protein for energy, rather than for tissue synthesis. Our experiment was designed to determine to what extent protein could be used for growth when the caloric intake was inadequate. Fifty-two groups of six rats each were fed dextrose and isocaloric quantities of mixtures of dextrose and protein hydrolysate (amigen®). Adequate vitamin and minerals were supplied. Weight changes, water intake, and the final body composition of normal, protein-depleted, calorically restricted, and scalded rats fed 10, 20, 30, or 50 calories daily for five weeks were observed. At all levels of caloric intake the protein-depleted animals receiving nitrogen gained more weight, or lost less weight, than the groups receiving dextrose alone, and total body protein paralleled the weight changes. For example, when fed 10 calories (one-third the caloric need) as dextrose they lost 16 gm., but with the same calories as dextrose and amigen® they lost only 4 gm. Similar differences, of greater magnitude, were observed at each caloric level and with each series of animals. Further studies of the ratio of protein to carbohydrate to produce best growth at each level of caloric intake are in progress.

Effects of Long-Continued Treatment with Cortisone in Patients with Congenital Adrenal Hyperplasia. Dr. Lawson Wilkins and (by invitation) Dr. Samuel H. Silverman, Dr. John F. Crigler Jr., Dr. Lytt I. Gardner and Dr. Claude J. Migeon, Baltimore.

Twenty patients with congenital adrenal hyperplasia have been under continuous treatment with cortisone for periods up to 23 months. Their ages when treatment was begun varied from 11 weeks to 18½ years. There were 13 females with pseudohermaphroditism and 7 males with macrogenitosomia praecox. In all cases it was possible to maintain suppression of the urinary 17-ketosteroids with doses of cortisone which caused no toxic or abnormal metabolic effects. The maintenance dose of intramuscular cortisone ranged from 6 mg. a day for young infants to 25 mg. a day for older patients. From 12 to 75 mg. a day was required when cortisone was given orally. Of six girls treated at 8 to 18 years of age, all have shown feminization, and four have menstruated. There has been decreased virilization and hirsutism. The older boys have shown under treatment adolescent-male sexual development with maturation of their testes. The younger children have shown cessation of virilization and decrease of their excessive somatic growth. In three patients with hypertension, the blood pressure has decreased concomitantly with the urinary 17-ketosteroids. Four children who had symptoms of severe sodium loss required, in addition to cortisone, treatment with a high sodium intake with or without desoxycorticosterone.

DISCUSSION

Dr. Samuel Z. Levine, New York: This method of treatment for the adrenogenital syndrome has been popularized by Dr. Wilkins and proved to be effective in many clinics. I should like to ask his opinion as to whether the administration of cortisone to a patient with the syndrome can differentiate between tumor and adrenal hyperplasia.

DR. NELSON K. ORDWAY, New Orleans: As I recall Dr. Wilkins' comments last year, they indicated that prolonged use of cortisone did not appear to interfere permanently with adrenocortical function as shown by ability to respond to corticotropin (ACTH).

I noticed on the slide data including the administration of corticotropin, some of which seemed to show that there was little rise in the excretion of 17-ketosteroids. I wonder whether, on the basis of his prolonged observations, Dr. Wilkins has evidence as to the ultimate effects of cortisone on the adrenal cortex.

DR. NATHAN B. TALBOT, Boston: First, I should like to state that the experience of my group is in complete agreement with that reported by Dr. Wilkins. Second, there are two questions which, perhaps, he would care to answer. One relates to what one may expect in male patients with this disease. We have observed one boy with congenital adrenocortical virilism who went through a seemingly normal adolescence, with testicular development, and on biopsy showed histologic signs of spermatogenesis when he reached the age of 10. I should be interested to know whether we should consider this case exceptional or whether Dr. Wilkins has made similar observations. If he has, what are his thoughts concerning the use of cortisone in treatment of male patients with this disease?

The second question relates to what may have been between the lines in Dr. Wilkins' paper. Did he wish us to infer from his remarks that the adrenals of these patients may indeed be producing an abnormal agent, one not produced perhaps by the ordinary normal person? That would have interesting implications with regard to the generally used term "adrenocortical androgen." Do the adrenal cortices of the normal person ordinarily secrete androgens?

DR. HENRY L. BARNETT, New York: I should like to point out that the importance of the observation, first made by Dr. Wilkins, that cortisone could be used for this purpose is perhaps fully apparent only to those of us who have cared for one or more patients with this condition.

I might also mention that Dr. Ephraim Shorr has observed a young woman with the adrenogenital syndrome who, after three or four months of receiving cortisone, became pregnant.

DR. BRUCE CHOWN, Winnipeg, Man., Canada: The one condition in which adrenal hyperplasia commonly occurs is erythroblastosis. The histology of the glands is quite different from that seen in the syndrome Dr. Wilkins has been discussing. In contrast to this syndrome, too, in some cases of erythroblastosis there is massive edema instead of acute salt and water loss.

I have wondered whether the adrenal hyperplasia of erythroblastosis, which sometimes can be tremendous, is the result of stress in the later part of fetal life and whether it is possible that stress in early embryonic life is the factor which produces the familial type of hyperplasia, in which Dr. Wilkins is interested.

Thinking along the line of blood groups, I wondered, again, whether the familial type is perhaps due to ABO or other incompatibility between embryo and mother, with an effect very early in embryonic life, and whether Dr. Wilkins has observed families—I am sure he has—in which a blood-grouping study could be carried out.

DR. LAWSON WILKINS, Baltimore: Dr. Levine, we feel that the response to cortisone is most valuable in differentiating adrenal tumor and hyperplasia. We have not seen any case of tumor in which the ketosteroids have been reduced by the administration of cortisone, and we have not seen any cases of hyperplasia in which there has been failure of suppression. Incidentally, our most recent patient is a girl with acquired adrenal hyperplasia beginning at 5 years, with all the symptoms one would expect with tumor. The ketosteroids responded to cortisone. Exploration did not reveal a tumor.

A question was asked with regard to regression of the size of the clitoris. We have not noted a definite decrease of size. We do see a marked decrease in the tendency to erections. There have been several cases in which painful and prolonged erections of a clitoral stump disappeared after administration of cortisone was begun.

Dr. Ordway asked whether it is possible that the offending adrenals may be permanently suppressed so that eventually therapy may be withdrawn. Two months ago I would have said I did not think permanent suppression was possible. We have had recently several cases in which, after a year and a half to two years of treatment, we have omitted cortisone and have seen a rise of 17-ketosteroids to only 12 or 14 mg., whereas prior to treatment the output had been 30 to 40 mg. We have also administered corticotropin (ACTH) after omitting cortisone

without increasing the ketosteroids to the pretreatment level. I have not discontinued treatment permanently in any cases. Perhaps after two, three, or four years of continuous treatment, cortisone can be decreased or stopped entirely.

Dr. Talbot asked some interesting questions about the male patients. The untreated male, although he develops all the secondary characteristics of adolescence, does not undergo complete maturation of the testes with spermatogenesis. In many cases the testes remain small, although in some cases they become infiltrated with aberrant adrenal tissue. The male patients who before treatment have reached a level of somatic development comparable to that of puberty (i. e., they have a bone age of 12 to 13 years) when treated with cortisone rapidly go into normal adolescence, with growth and development of their testes. When treatment is started at a younger developmental level the progress of sexual development is checked. It is open to question whether it is desirable to treat the older males with cortisone. I do not think fertility is especially desirable in persons with a disease that has such strong familial and genetic possibilities. In the younger patients, our main objective is to suppress precocious osseous development and early epiphyseal fusion, which result eventually in stunted growth. It is desirable to treat the patients as young as possible.

The question about the action of the adrenal on the salt loss is of interest. We believe that in this condition there is an abnormal pattern of adrenal hormones which has a tendency to cause sodium loss. We do not know whether there is some particular salt-losing steroid. Some early work of Dr. Darrow's and some of Dr. Barnett's suggest that adrenal androgen might block the effect of other hormones on the reabsorption of sodium by the kidney.

I am delighted to hear about the recent pregnancy in New York. Do not hold that against me!

I am afraid I cannot discuss very thoroughly the relation of erythroblastosis to congenital adrenal hyperplasia. The familial incidence of this disease is well known. Dr. Gardner has been making studies of the family trees, blood groupings, and other genetic traits in the families of our patients.

Dr. Lytt I. Gardner, Baltimore: I think I can add to the interesting idea that was presented concerning the possibility that congenital adrenal hyperplasia might be an ABO sensitization phenomenon. Unfortunately, we do not find this to be the case so far as our data are concerned. We have been attempting to gather information which might enable someone some day to evaluate the results with respect to whether or not any one datum on a patient might link genetically with the occurrence of the affected child in families with congenial adrenal hyperplasia.

Hence we started collecting data on blood groups and on the various other easily measured factors which are known to be inherited, such as the ability to hyperextend the terminal joint of the thumb and the ability to twist and curl the tongue.

In three families, in which we have as complete blood-grouping studies as we can obtain, there has been no evidence of close linkage among any of the groups. The general appearance of the family trees suggests a simple Mendelian recessive trait. I think further collecting of data of this sort is most important.

Developmental Status of Children with Birth or Minimal Postnatal Weights of One Thousand Grams or Less. Dr. Margaret Dann (by invitation), Elizabeth New (by invitation), and Dr. Samuel Z. Levine, New York.

Despite published reports, the developmental status of surviving premature infants remains a controversial subject. For this reason, a follow-up study was undertaken of 94 children who weighed 1,000 gm. (2 lb. 3 oz.) or less at birth or in the neonatal period and who lived to be discharged from the premature unit of the New York Hospital from 1940 through 1951. The birth weight of 42 of these children was under 1,000 gm.; the remaining 52 children weighed between 1,000 and 1,300 gm. at birth, but their postnatal weight declined to 1,000 gm. or less. The survival rate for the entire group was 29% (94 of 328).

Of the 45 children who have reached the age of 3 years or more, 28 have thus far been given an examination comprising detailed measurements, physical examination, eye examination, and psychometric testing and social evaluation. All psychometric examinations have been made by the same psychologist. Of the 28, 20 have had previous examinations in the pediatric outpatient

department, including a number who have attended regularly since discharge and 7 who have had more than one psychometric test. In addition, 8 of 10 full-term siblings ranging in age between 3 and 12 years were examined.

The results thus far obtained suggest that aside from eye defects tiny premature infants who survive usually attain a physical and mental status of development which parallels that of the general population.

DISCUSSION

Dr. Randolph K. Byers, Boston: This is a splendid study and one that needs to be carried out thoroughly and probably ought to be carried out thoroughly in a good many places, under a good many circumstances.

There are several words of caution that I should like to speak. I remember a child at Children's Hospital a long time ago—he is 28 or 29 now—who weighed 2 lb. (907 gm.) at birth, grew up in a very anxious home, and was seen by me at 3 years because he was not talking. Studies revealed that he had enlarged ventricles. His IQ was low. His mother had had toxemia; I do not know whether that had anything to do with delaying his development. The odds looked all against him at that time, but he later graduated from Dartmouth and became a colonel in the army and is quite a fellow.

In measuring acute cortical injury, such as might be produced by anoxia, the IQ probably is not a good indication. Damage has to be severe to show up in that form of measurement, and I think that learning power and attention, which are not measured well by the Stanford-Binet test, are much more important in relation to diffuse cortical injury. The learning capacity in school is the item we are going to need to know most about.

Dr. Milton J. E. Senn, New Haven, Conn.: The clinician is constantly called upon to predict the outcome of a disease or the development of a human being. He is on firmer ground or feels more secure in predicting the natural history of disease than in predicting the natural history of a live human being, because more is known about diseases and disease processes than about the development of the human being and how he functions.

It seems to me that the value of this work by Dr. Dann and her associates lies in the attempt to study a particular type of human being, one born prematurely. Such studies are extremely difficult and more hazardous than those dealing with tissues and cells, but since our need for more information about the human being is so great, I am hopeful that there will be more such studies.

Dr. Richard L. Day, New York: Squint is often seen in babies who have a mild residual retrolental fibroplasia in one eye. I wonder whether the babies with squint might not have had that disease.

Dr. Alfred H. Washburn, Denver: I, too, am delighted to have somebody get started on a study of this sort, and certainly I am tremendously pleased to have the study going along the line described by Dr. Byers and Dr. Senn. I should like to add a comment based on experience with the Stanford-Binet test. To help us understand what is happening dynamically in a particular child, it seems to me that more will be needed in this study not only in terms of measure of achievement, learning, and so on, but also in terms of our need to be able to predict future behavior. I am a little distressed and wonder whether it might not be possible, in this study as well as in others, to start some of the projective techniques before the age of 3 years. I have an idea that when you start studying the learning process and other functional achievements later on, you are going to wish you had such material obtained before the age of 3 years.

Dr. Myron E. Wegman, New Orleans: There was a sizable discrepancy between the number of males and the number of females in Dr. Dann's groups. I hope in further analysis they will take account of the fact that the 22 females in all likelihood represent a higher percentage of more mature infants than the 7 males, so that the two groups are not entirely comparable.

Dr. Hugh McCulloch, Chicago: I was interested in the concentration of residual vision in the eye. It might be expected. I should like to ask whether the persons who did not attain normal stature in later years might have had some congenital anomaly, cardiovascular or other, as a retarding influence.

DR. MARGARET DANN, New York: I am grateful to everyone for their comments and questions. In regard to what Dr. Byers asked, I think we are well aware that a single test, particularly at as early an age as 3 years, is only the beginning of an answer. In fact, to comment on Dr. Washburn's question in connection with this observation, we should like very much to test a number of these children at an earlier age, as well as to continue, as we are planning to do, serial studies, getting each child back at yearly intervals.

The oldest child in the series is 10 years of age; so we cannot say even yet that any of the children who have not attained normal height and weight are eventually going to be stunted. There is no relation between the subnormal height and weight and other congenital anomalies.

The eyegrounds of all the children except one, who was uncooperative, were examined by members of the staff who have had considerable experience, and there was no evidence of residual retrolental fibroplasia in any of the children with squint except those I mentioned who showed evidence of the disease.

We should like very much to use achievement tests and other tests. We have occasionally used another test in addition to the Binet, but only in isolated cases in which we ran into difficulties. One child who had some emotional difficulties was given a Rorschach test. A Merrill-Palmer test was used on a 4-year-old nearly blind child on whom we felt that neither test was satisfactory.

The comment about the greater incidence of females and males in our series is pertinent. It fits in with the well-known fact that the female child of the same weight has a better chance of survival, statistically, than the male child, and we think the better chance is definitely associated with greater maturity.

I should have mentioned also that five of the children in our study were twins. In each case, unfortunately, the other twin died. We might feel that the five whose premature birth was associated with twinning were more mature for their weight than the weight itself would indicate. However, we did not find that either in regard to twins or in regard to differences in sexes there was a great deal of predictability as to how well a particular child would do in comparison with the others.

Psychiatric Aspects of Changes in Infant and Child Care. DR. HILDE BRUCH (by invitation), New York.

During the past three decades child-rearing habits have undergone radical changes. Several opposing influences can be recognized, each claiming to be "better" for the ultimate health of the child. Although outwardly very different, often diametrically opposed, the various recommendations have in common that they are taught as definite "techniques" to improve the child's physical and mental health. The recent development, largely under the influence of psychiatric teaching, has been in the direction of "permissive" techniques as opposed to "rigid" child care.

This paper is concerned with the critical evaluation from a psychiatrist's point of view of the validity and meaning of the various recommendations, such as rooming-in, self-demand versus schedule feeding, early versus late toilet training, permissive attitude versus discipline, and so on. The many behavior difficulties and adjustment problems which are encountered in children in spite of, or sometimes on account of, these changing child-rearing habits can be related to factors inherent in these changes or the need for such changes. Although much lip service is paid to the importance of the parents' feelings and attitude, changes and recommendations are often introduced without any consideration for the parents' personality and life experiences. In this way any "technique" may become harmful, regardless of its form or content. Some basic factors must be recognized if "changes" are to be beneficial. It is essential for the pediatrician to recognize and deal objectively and with awareness with these underlying factors if he wants to utilize to the fullest the possibilities of his position as family adviser during the early life of a child.

DISCUSSION

DR. A. ASHLEY WEECH, Cincinnati: I like the statement that children are individuals and so are parents, and that no formula can be made that will apply to all children in all families without producing disastrous results. This statement means that the pediatrician somehow is

going to have to find more time to study his families. I wonder whether Dr. Bruch has for the harried pediatrician, who is seeing patients all day, any advice on how to select the occasional ones who most need this type of individualized treatment.

DR. ALFRED H. WASHBURN, Denver: I cannot resist saying how delighted I am to hear somebody talk about the dangers of complete rigidity in the application of permissive philosophy. We have been tremendously impressed in our region with the fact that some of the pediatricians and parents who have embraced the new fad of permissiveness most vigorously are far and away the most rigid in their insistence that everyone follow this so-called permissive regimen.

DR. ANGUS M. MCBRYDE, Durham, N. C.: As one who has been practicing some of the permissive techniques for about five years on the compulsory basis, I feel that Dr. Bruch's unconscious throwing of darts is hitting in my direction.

I should like to say that my experience of regimenting mothers to the extent of compulsory rooming-in, which might include the beginning of the child's experience, has convinced me that Dr. Bruch is perfectly right in condemning this attitude. I have found that a certain number of mothers, because of their emotional endowment and past experiences, are not able to take rooming-in.

Some of us who are enthusiasts for rooming-in feel that it is good technique for the first and second child, and perhaps for all the others, provided the one condition I should like to stress is carried out; that is, adequate education before the mother goes to the hospital. Adequate education in the permissive techniques is important before they are forced by the mother.

DR. CHARLES HENDEE SMITH, New Brunswick, N. J.: A man took his 7-lb. baby home and was told to feed it "on demand." At the end of 22 hours he called the hospital and said, "We have given two days' formula already and are starting on the third. What shall we do when that's gone?"

I mention this incident as an example of the permissive, or demand, schedule being carried to an extreme.

Personally, I am an old shellback who believes that some guidance and discipline is better for children than their own free will. I think the middle ground is the one that we should follow.

DR. HILDE BRUCH, New York: I wish to thank the discussants for their comments and questions. An answer to Dr. Weech's question as to how to select patients who need individual treatment would require a new and different paper. I did not speak about selecting patients for individual psychiatric treatment but about the need of each mother and child for individual appraisal as to whether they will do better with disciplined and directive or permissive techniques. It should be part of pediatric training to learn to determine in a simple interview, not in a psychiatric study, whether a mother functions better as an obedient child or an independent person. Instructions should be geared according to such observations.

Dr. Washburn stated clearly what I had intended to convey, that it is not the technique that counts, but how parents interpret it. It is, in my experience, common that permissiveness is rigidly applied.

I have no quarrel with Dr. McBryde except with one basic idea. I do not think that rooming-in and permissiveness are identical. I think rooming-in is a beautiful practice. As a matter of fact, it is about as old as humanity and had only a brief interruption in modern American hospitals. I might use my own background as an example. Nobody can accuse Prussian education of being permissive, but rooming-in was the rule. Unless there was real urgency, nobody during my childhood had a baby in the hospital.

It is not rooming-in that is emotionally confusing. It is the emotionally overcharged atmosphere with which it has become connected, the rhapsodic song of "a team started right from the beginning." That "team" started much earlier. Rooming-in may be a really good method, a natural expression of human relationship. However, as I have seen in some of my high-class New York patients, it may turn into a dreadful showpiece of artificial affection. This seems to me the danger—that it will become a demonstrable and talked about "special thing" of having superior maternal feelings.

Rooming-in in itself has nothing to do with permissiveness. The same statement applies to what is called self-demand feeding. That, too, is a method with which I have been familiar since childhood. But, as I have said, Prussian education otherwise was anything but permissive. Such things are not necessarily connected.

I agree with Dr. Smith that self-demand feeding may lead to overanxious handling. Its success depends on the personality of the mother and on her having someone to help her understand why a baby cries, that there are other reasons for crying than being hungry.

Collaboration Between a Children's Hospital and a Psychiatric Clinic for Children in the Treatment of Ulcerative Colitis. Dr. Andrew D. Hunt Jr. (by invitation), Dr. John A. Rose (by invitation), Dr. Meyer Sonis (by invitation), Sylvia Glasner, M. S. W. (by invitation), Mildred Berg, M. S. W. (by invitation), and Jane Poptowski, R. N. (by invitation), Philadelphia.

The case of a 14-year-old boy, in addition to being the history of a patient with severe ulcerative colitis, traces the development at the Children's Hospital of Philadelphia of a collaborative approach to patients in whom emotional problems play an important part in the clinical picture, an approach utilizing all the professional disciplines involved in the child's care.

The great difficulty in the hospital management of such patients has always been that of coordination of the efforts, approach, and points of view of the various people involved. The pediatrician has not known what the psychiatrist was doing in therapy; conflicting ideas have not been discussed professionally; the observations of nurses, residents, and other ward personnel have not been utilized to their fullest extent; and their attitude to the patient may not always have reflected the ideas of the persons in charge of the case. Around this patient a technique of effective collaboration was developed. The pediatrician first saw the need for psychotherapy, and his initial role was that of indoctrination of the parents and building up of a feeling of need for psychiatric assistance. By conferences with the Child Guidance Clinic group, arrangements were made for therapeutic interviews with both parents and child. Once such therapy had begun, weekly conferences attended by the pediatrician in charge, resident physicians, nurses, psychiatric social workers, and psychotherapists were held so that a common point of view was maintained. Each observer was kept informed as to the progress the others were making. Necessary medical care and procedures had to be carried out in such a fashion as not to play into possible secondary gains on the part of the patient. Collaboration was so carried out that neither pediatrician nor psychiatrist felt his role in the case threatened by the other's participation.

The results were most gratifying, and this technique is being established as a pattern for dealing in the future with similar cases.

The case itself is a most interesting one. A fulminating, febrile, rapidly wasting, and potentially lethal illness developed after three years of gradual onset. The usual medical regimens had failed. Corticotropin was given for one month and accomplished nothing except lowering of the temperature. After tapering of the dose and withdrawal of corticotropin and following his second psychotherapeutic interview, an acute episode requiring laparotomy and appendectomy occurred. Later, after psychotherapeutic interviews were taking place twice weekly, there was a sharp improvement in the stool picture but simultaneously there appeared huge ulcerations of the skin. (Kodachrome® slides were shown.) Within a few months both the skin and the bowel healed completely and the child was able to return to school.

The psychopathology of this case has been well worked out, is characteristic of this disease, and is essentially similar to that seen in younger children.

It is planned to divide the alloted time for presentation with the pediatrician, who will describe the medical aspects and the nursing problems, and the psychiatrist, who will discuss the part played by him and the psychiatric social workers.

DISCUSSION

Dr. Milton J. E. Senn, New Haven, Conn.: It is not my purpose to discuss the psychogenesis of this case of ulcerative colitis, or to discuss what I believe may have been instrumental in the satisfactory therapy, but rather to focus on the collaborative efforts of the Children's Hospital in Philadelphia and the Philadelphia Child Guidance Clinic.

As an outsider, yet in a way an insider, I should like to present some of the history of the collaboration between psychiatrists and pediatricians in such important centers.

The problem of successful collaboration is still not settled throughout the country. Beginning in the 1930's, when the importance of psychiatry began to be recognized by pediatricians, pedia-

tricians frequently attempted to form a collaborative relationship with psychiatrists, only to meet with some interference. Although at Johns Hopkins the child guidance clinic was established within the department of pediatrics, not until recently was there a close and satisfactory relationship between such departments in other centers.

In Philadelphia, I had the interesting opportunity of seeing how this collaboration developed. It seems to me that it came about because, first, the pediatric staff of the Children's Hospital not only understood its own psychiatric needs but tried to develop within the framework of pediatrics the psychiatric help that was needed. Second, the psychiatric staff in the guidance clinic was willing to leave the walls of the clinic, go into the Children's Hospital, and learn at first hand how to help the pediatricians carry on a better kind of child care program without becoming psychiatrists.

I should like to pay tribute, then, to the abilities of both the men in psychiatry and those in pediatrics to break down departmental barriers, to come together in a program of mutual interest within the framework of pediatrics. I think one of the reasons for the success of this collaborative venture is the fact that a pediatrician (Dr. Joseph Rudolph) had the opportunity of being trained in the Philadelphia Child Guidance Clinic, not as a psychiatrist but as someone who might have a better understanding of how a psychiatrist works, and then went back to the Philadelphia Children's Hospital to continue to work as a pediatrician, with new insights gathered from the guidance clinic.

DR. LITTLE: I had an opportunity in February to see the entire group who had taken part in this case and to discuss it in some detail. This was one of the most stimulating and thrilling experiences I have ever had.

The point Dr. Senn made about the collaboration in this case bears considerable emphasis. Ulcerative colitis happens to be a condition in which without good collaboration there is a fair chance of the patient's dying. Innumerable cases go through our hospitals in which without collaboration the patient survives, but if we could begin to have in treating a great many other conditions the kind of collaboration which was present in this case we could do a much more effective job.

I want to describe an experience with a similar child. At the time of my hearing about the case reported there had been in our hospital for two months a boy who had come in with a perforated colon, had had an ileostomy, and subsequently had had a colectomy. He had gone progressively downhill.

Hearing about the work here described stiffened my backbone and gave me a kind of conviction which I had not had before. My colleagues and I then organized the kind of collaborative approach which we thought we had had before but were not really approaching. And with our being able to do that, to our considerable amazement some rather dramatic things happened.

The mother, who was a very conscientious person, much the kind that Dr. Rose described, had been staying night and day with the boy. Having been given an opportunity to understand her feelings about having to be at the hospital, she was able to realize what was happening to the rest of her family in the meantime and decided to go home and come back in two or three days to help take care of the boy again.

Within a half-hour of her leaving, the boy, who had had fever and considerable abdominal pain, had begun to improve. Within 24 hours, he was up and around, helping the nurses in the ward. Three days later, when his mother and father returned, within a half-hour he was back in his original condition. That experience was fairly convincing to us.

Subsequently the situation improved. We have not done as satisfactory a job as the one reported, but we have made some progress in the right direction. The boy has gone home and is doing fairly well.

The point I want to make is that I think all of us, including those who think we have some psychiatric orientation, often need something to give us a sense of conviction about a situation of this kind, because we see ulcerative colitis as an exceedingly severe physical illness, probably complicated by emotional factors, but we wonder whether there is some factor X of which we are not aware. I think this feeling has blocked us against going ahead in an effective fashion to handle such situations.

DR. A. ASHLEY WEECH, Cincinnati: I think a pediatrician who is not psychiatrically oriented should also have a word to say on this subject. What is now going on in Cincinnati is a direct outgrowth of an attitude passed on to Dr. Richard Wolf by Dr. Milton Senn; we are grateful to him for it.

We have a system there which permits any responsible person who becomes concerned about the behavior of a chronically ill child in the hospital to request a conference. The conference, when it is held, is presided over by the pediatric psychiatrist but is attended by nurses, by the school teacher, by the social worker, by the play teacher, by the resident, and by others. Suggestions are received from all concerned as to what can be done to improve the child's attitude toward his own illness and to prepare the way for his return to his own home. These conferences have gone a long way toward meeting what we can call the over-all needs of a child in a hospital.

DR. HILDE BRUCH, New York: I have a question to ask, namely, how far was the hospital setup, the routine of the hospital, used in the environmental therapy of the child?

The description was of a child with an insatiable demand to have his way, though, as Dr. Rose pointed out, at the same time the child was in fear. The parents, as well as one of the residents, were disgusted with the child's behavior. How was, on the whole, the setup of the hospital used in treatment? How far were these insatiable demands satisfied, and when was the hospital setup used as a starting point for developing a concept of self that was not in such complete isolation?

DR. ANDREW D. HUNT JR., Philadelphia: We thank Dr. Senn and the others for their comments. Dr. Bruch's question is certainly for Dr. Rose rather than for me.

However, I should like to point out that this boy did not actually begin to improve until the entire group worked together on the problem. Perhaps the most important element was the nursing staff. As I pointed out, at first the girls found themselves, as they phrased it, "over a barrel." The boy had them "coming and going." We finally got to the point that they could, in a kindly, understanding fashion, tell Bill that it was his own responsibility to use the bedpan, that it was up to him to clean the crusts from his sores in the bathtub, and so on.

In short, when Bill was enabled to assume some of the responsibilities for his own recovery, improvement began to become apparent.

DR. JOHN A. ROSE, Philadelphia: Dr. Bruch wishes to know if we feel that a psychotherapeutic milieu has been created in the hospital ward. We feel that such a milieu is created, not directly, but as a by-product of the sensitive exploitation of the values of the various professional roles in the ward. For instance, rather than encourage a nurse to operate as a psychotherapist, we try to help her to do what she ordinarily does in a more spontaneous and helpful way. This is to say that the same factors come into play with nurses as with parents. One does not teach them a didactic psychological language, but rather strengthens their basic assets in the performance of their jobs. The psychological problem of the child is mentioned chiefly for the purpose of helping professional personnel to avoid playing into its destructive aspects. We feel it is an important principle to affirm that each professional person has a particular job and that there are particular psychological values to this job. In this way and by stressing the fact that we must all work together, we try to avoid competition for close relationship with the child. We also hold regular conferences in order to increase our communication with each other so as not to be working each in an isolated sphere.

In summary, we try to preserve the spontaneous values of the individual contributions of all persons concerned, while trying to help them to preserve these values without their operating against other professional personnel, and certainly without their operating against the interests of the child and family. To the degree that we are successful in stimulating and coordinating these aspects of hospital-family function, we are successful in the creation of a therapeutic milieu.

Peptic Ulcers in Childhood. DR. BERTRAM R. GIRDANY (by invitation) and DR. STUART STEVENSON, Pittsburgh.

Thirty-five infants and children studied at the Children's Hospital of Pittsburgh during the past year have shown clinical and x-ray signs of peptic ulcer.

In two instances when obstructive signs were marked the diagnosis was confirmed by direct surgical exploration. The remaining patients, in addition to diagnostic clinical and x-ray findings, have shown good response to ulcer therapy.

Although peptic ulcer is considered a rarity in pediatric practice, preliminary studies indicate that the incidence of the condition is high. Moreover, certain personality traits and factors in the home environment of the children observed tend to fit a fairly uniform pattern.

Clinical and x-ray data were presented, with some discussion of the range of clinical complaints and some preliminary observations on the problems of peptic ulcer diagnosis and therapy in pediatric practice.

DISCUSSION

DR. STUART S. STEVENSON, Pittsburgh: When Dr. Girdany began finding these duodenal ulcers, I had difficulty believing in them and he was dubious himself. When he observed 45 in one year, we had to take stock of what was going on. This was a much higher incidence than was reported anywhere in the literature. We tried to think of possibilities to explain the high incidence. One is that he was wrong, which does not seem likely: He has enumerated the criteria he used for making the diagnosis. Another is that ulcers are more prevalent in Pittsburgh children, possibly owing to unstable labor conditions. A third is that we have not recognized these ulcers before because we have not looked for them. Many of the children had pain at a time when it might be judged to be psychogenic: Two children had pain when they started school, and two children had pain when new siblings came into their families. The fourth possibility is that there is actually a higher incidence. The children were postwar babies, and perhaps the disease is increasing.

A word about the vomiting Dr. Girdany spoke of. The younger patients were presented for examination with a complaint of vomiting, and pain was not mentioned. Five of them had a typical story of cyclic vomiting; perhaps we should worry more about the possibility of duodenal ulcer in connection with so-called cyclic vomiting.

We should like to know a lot more about birth histories of these babies, their early feeding in infancy, their toilet training, and so on. I do not think Dr. Girdany said anything about these points. Two children who were questioned had early forced toilet training. I am sorry the subject was not gone into with the others. There is certainly a great deal of further work indicated. I think the paper suggests that we must take better histories of children with abdominal pain and vomiting. Much pertinent background material was not offered by the mothers and had to be elicited by questioning.

I think we should cooperate more with internists in trying to work out life histories of patients with duodenal ulcer. We have been more and more impressed, as we reviewed the literature, with the fact that many patients start their ulcer stories in the first decade of life. Perhaps with such cooperation a more coherent life history of this disease can be constructed.

DR. ANDREW D. HUNT JR., Philadelphia: I should like to emphasize the fact that in such children personality structures of the sort described by Dr. Girdany are typical. My group has recently seen a 12-year-old boy with a duodenal ulcer whose story was similar. He was an extremely quiet child, withdrawn, and shy and passive in his relationships with other children. He rarely played with them; most of his spare time was spent by himself. He had a brother three years younger who was an aggressive, vigorous child and who was rapidly approaching our patient in size and weight. There was a great deal of conflict around this situation, which was constantly being intensified by such remarks from the parents as "Frank, if you don't eat, your baby brother will soon be able to beat you up." The parental response to the boy's abdominal pain was most interesting. For many months this pain awakened the child at night. The mother's way of handling the situation was to go into his bed, lie down beside him, and massage his abdomen until he went to sleep. Thus the elements of secondary gain were very strong.

On superficial examination this boy, as is so often the case in situations of this sort, did not appear the least bit "nervous." Such outer calm and extreme cooperation during a physical examination can throw the pediatrician off guard, since a child who is easy to examine is a rare treat for the busy practitioner. The history of an inability outwardly to express emotional problems and conflict, together with this passive cooperative appearance, is often a clue that complaints are psychosomatic in origin.

Observations of this sort can frequently be extended to the common symptom of abdominal pain in childhood for which no organic cause can be found. Such abdominal pain is certainly one of the commoner problems confronted in pediatric practice, and we have found that a rather high percentage of children with this presenting symptom have the same kinds of personality difficulties as those mentioned.

Finally, since peptic ulcer is almost universally accepted as a disease whose origin is at least to a large extent on an emotional basis, I should like to make a plea for the consideration of emotional factors not only in the diagnosis but also in the treatment of the condition.

DR. FREDERIC N. SILVERMAN, Cincinnati: I am not certain whether we should commend Dr. Girdany for finding so large a group of children with peptic ulcer or whether we should condemn the rest of us for not finding ulcers. I fear the latter possibility may be more likely, because recent reports in the roentgenologic literature indicate that ulcers are not uncommon in childhood.

The experience in Pittsburgh, however, is at variance with the experience in our department in Cincinnati. This is true even though the diagnosis of peptic ulcer is being made for children in other departments in the city where adults are examined as well as children. I have often thought that the local discrepancy in results was the result of differing approaches of orthodox radiologists and those of us who have been called "radio-active" pediatricians.

Except for a few classic ulcers in children in the second decade, we have recognized peptic ulcer only in children who have had burns, head injuries, surgical correction of what has been called congenitally short esophagus, and, in one case, rather vigorous administration of calcium chloride by mouth.

The x-ray diagnosis, which has been shown so ably by Dr. Girdany, is helpful confirmatory evidence and is based largely on the demonstration of the niche. Had Dr. Girdany more time, I am sure he would have pointed out that the persistence of the ulcer niche is important in the x-ray diagnosis. Many of you may have seen little irregular shadows that looked much like the ulcers shown on the slides in films of children who clinically did not have ulcer. These shadows disappear when watched under the fluoroscope or are found only in one of a series of films, whereas the true ulcer shadow persists.

The associated signs of spasm and hypermotility of the bowel do not by themselves warrant a diagnosis of peptic ulcer, but when coupled with a good clinical history may lend support to the diagnosis.

I might add that we have seen children with Meckel's diverticulum who have periumbilical pain and some blood in the stools, and these children, of course, do not show x-ray evidence of peptic ulcer. We have wondered how many children with these complaints who do not fulfill the x-ray criteria for the diagnosis of peptic ulcer and who do not come to operation may actually have Meckel's diverticulum or even a duplication.

DR. IRVING J. WOLMAN, Philadelphia: Were gastric analyses done with these patients? If one looks through the literature on peptic ulcers in childhood, one will be surprised to find that almost no author reports the results of gastric analysis. It would be very important, with a large series like this, to know whether the children have hyperacidity. The internists and gastroenterologists rely on this finding in practice with adults. It would be most helpful in a series of childhood cases like this, in which the ulcers have apparently been proved by x-ray or surgical exploration, if data had been gathered on the status of acid production in the stomach after histamine stimulation. Should a high rate of correlation be found, the average pediatrician might prefer to do a gastric analysis first as a screening procedure in a suspected case, rather than to order immediately an x-ray series. This procedure would be considerably less expensive and time-consuming, both to the hospital and to the patient.

DR. BERTRAM R. GIRDANY, Pittsburgh: I should like to thank every one for his comments; it is good to have Dr. Hunt confirm our observations on these children.

Dr. Silverman poses an important question concerning the high incidence of peptic ulcer in our experience. I have not a complete answer. Dr. Stevenson has offered some pertinent comments.

I would emphasize, however, that the roentgenologist must not always be accorded the final word in diagnostic problems. When there are clinical data to support the diagnosis, and the findings on x-ray examination are not inconsistent with them, a trial of ulcer therapy is indicated.

There are technical difficulties inherent in handling children that may preclude completely satisfactory x-ray examination. It may be that these difficulties comprise one factor responsible for less widespread recognition of the condition.

In answer to Dr. Wolman, we have not obtained gastric analyses for our patients. Internists and radiologists handling adult ulcer patients place small reliance on the test by itself, although it does have limited usefulness. Studies are in contemplation, in cooperation with Dr. I. Arthur Mirsky, along the same lines as those carried out on adults, to see whether these children fall into the class of "hypersecretors." They will be reported on at a later date.

Pressure-Time Relations in Safe Correction of Atelectasis in Animal Lungs. Dr. Richard Day, Dr. Alice Goodfellow, Dr. Gustav J. Beck, and Dr. Virginia Apgar, New York.

Smith and Chisholm found that infants can exert 50 cm. of water negative pressure on forceful inspiration. It is a paradox that others have found that positive pressure resuscitation may injure the infant lung and yet fail to correct atelectasis at pressures as low as 20 cm. of water. A customary recommendation is 12 to 15 cm.

Could injury at low pressures arise from too long application of the pressure? The infant's first gasp is very brief and intense. When two rubber balloons are connected in parallel to an air system, pressures only moderately above the expansion threshold will inflate only one of them. High pressure inflates both, and the amount of distention is directly proportional to time. Time control prevents rupture.

Rat lungs were paired and substituted for the balloons. One lung was normal; the other was rendered totally atelectatic by administering 100% oxygen to the rat after administration of pentobarbital (nembutal®) and then occluding the trachea. Volume changes of the two lungs were separately recorded plethysmographically. No collapsed lung could be opened by pressures of 18 cm., and few at 20 cm., and yet the control lung was alarmingly distended and in one instance was injured. With time control, however, much higher pressure could be used without undue distention of the control lung and with success in opening the collapsed lung. The best results were obtained with pressures of 50 to 60 cm. applied for less than one-fifth second.

Preliminary tests of fetal piglet lungs seem to confirm the principle demonstrated by the rat lungs and the balloons.

An application to infants has not yet been made and should not be made until the safe time interval for effective pressures has been accurately determined on infant lungs.

DISCUSSION

Dr. Herbert C. Miller Jr., Kansas City, Kans.: I find Dr. Day's paper intriguing, as he has emphasized that the duration of inspiration in the newborn infant may be a very important matter. I should be hesitant to accept evaluations of this duration that were based on measurements of the chest movements or of the abdominal movements.

However, the measurement of air flow in and out of the nose and mouth of the baby offers an excellent means of measuring inspiration and expiration. My group has studied this problem in a good many newborn babies, and we have found that inspiration in many premature babies is of the order of one-tenth or two-tenths second, and expiration, three-tenths or four-tenths second. I would guess that the average duration of inspiration in newborn babies, both premature and full-term, is around two-tenths or three-tenths second.

Dr. Day has commented on the pressures used in the various mechanical devices to resuscitate babies. I am sure he has given considerable thought to the duration of the cycle in these devices, and I wonder whether he would be willing to comment on the duration of the cycle used in the commoner devices found in most hospitals.

Dr. Clement Smith, Boston: I have had the pleasure of seeing the careful work Dr. Day and his colleagues are doing in this field, and the further demonstrations, though he has shown the best today, are very convincing.

There is one other factor besides the too long application of the single puff under positive pressure that may rupture the lung under ordinary resuscitative procedure. This is the long repetition of puffs which are not in themselves effective. Most babies who come to autopsy

with ruptured lungs have been worked over for many minutes, often half an hour or more, in an unsuccessful attempt to start their breathing. If—and it is quite a big "if," on which I am glad Dr. Day is working, because no one will do it more cautiously and wisely—a device can be perfected which will provide a few minutes only of rapid, sharp gasps of an artificial nature for the human infant who cannot do them himself, the added risk of overprolonged application will also be prevented. I am sure that Dr. Day realizes the amount of effort that will have to go into safe application of this principle for its full profit to the human infant.

Pulmonary Hypertension with Persistent Patency of the Ductus Arteriosus. Dr. Helen B. Taussig and (by invitation) Dr. S. Richard Bauersfeld and Alex J. MacDonald, L.R.C.P., S. I., Baltimore:

Pulmonary hypertension and persistent patency of the ductus arteriosus produce such a distinctive clinical syndrome that the diagnosis may be made at sight. When the pressure in the pulmonary circulation exceeds that of the systemic circulation blood will flow from the pulmonary artery to the descending aorta. Consequently the feet will be more cyanotic than the hands. Inasmuch as the left subclavian artery arises close to the entrance of the ductus arteriosus, some venous blood from the pulmonary artery may be forced back into the left subclavian artery and the left hand may be more cyanotic than the right.

The increased resistance in the pulmonary vascular bed increases the work required of the right side of the heart. There results right ventricular hypertrophy. The increased force in the ejection of the blood combined with the high pressure in the pulmonary artery causes marked accentuation of the second heart sound and dilatation of the pulmonary artery. The base of the pulmonary artery may become so greatly dilated as to lead to pulmonary insufficiency. Inasmuch as the ductus arteriosus acts as an escape valve, the periphery of the lungs remains clear and often the heart remains small.

Any condition which produces pulmonary hypertension in the presence of persistent patency of the ductus arteriosus produces this clinical syndrome. In some cases the pulmonary hypertension appears to be primary, as the only cardiac abnormality is right-sided heart strain; in other instances the pulmonary hypertension is secondary to a malformation of the left side of the heart. The wide variation in the conditions which produce this distinctive clinical syndrome renders detailed investigation as to the underlying pathology imperative before the institution of any therapy.

DISCUSSION

Dr. Bertram R. Girdany, New York: Dr. Taussig mentioned in passing the electrocardiogram. I should like to know a little more about it. It would also be interesting to know whether the child on whom autopsy was performed showed the same changes in the lungs that the group of children reported on by Dr. Bauersfeld showed.

Dr. John M. Adams, Los Angeles: My colleagues and I have been interested in pulmonary hypertension and have studied a number of patients with patent ductus arteriosus and pulmonary hypertension. I should like to say at this point that a number of patients with patent ductus arteriosus have pulmonary hypertension, sometimes severe, without becoming cyanotic. One of our patients had a pulmonary artery pressure of 104 with a systemic pressure of 110. Thus he was not cyanotic.

I am wondering whether Dr. Taussig thinks this is the mechanism for the development of such pulmonary hypertension. I should also like to say that we feel quite definitely that the symptoms of children with left-to-right shunts are related to the pulmonary hypertension; that is, the dyspnea. However, children also have dyspnea who have pulmonary valvular stenosis without cyanosis. I should like to know Dr. Taussig's idea on the etiology of dyspnea, since these two conditions are quite different and yet the patients have dyspnea.

Dr. Robert Lawson, Winston-Salem, N. C.: This may be a show of ignorance, but I could not help wondering whether the operation of closure of the ductus is so bad in this situation. Is there any point in creating an artificial ductus in patients with pure pulmonary hypertension who are doing badly?

Dr. Hugh McCulloch, Chicago: It is important to learn that in patients who exhibit symptoms of pulmonary hypertension this lesion may be present.

Dr. Taussig's presentation made it clear that there are some physical signs that there may be a mitral lesion, and she mentioned the fact that these must be recognized before the patient is subjected to operation.

DR. HELEN B. TAUSSIG, Mt. Washington, Md.: Dr. Girdany, the usual picture of pulmonary hypertension with persistent patency of the ductus arteriosus is one of right-sided heart strain. Although the absence of a right axis deviation and right ventricular hypertrophy in the precordial leads does not rule out the possibility, it is the great exception, because the heart is pumping against the high pressure in the pulmonary vascular bed.

Yes, we have studied changes in the lungs. The baby that did come to autopsy had, as I said, a severe left-sided heart lesion and also had changes in the lungs similar to those described by Dr. Bauersfeld. We are still in a quandary as to whether there is a congenital abnormality of the lung or what is the cause of the primary pulmonary hypertension. The problem is interesting.

The question has been raised whether the pulmonary hypertension is due to a primary abnormality in the lungs. In the first cases studied in our clinic, Dr. Damman thought that the pulmonary hypertension was due to the excessive flow of blood through the lungs. Actually I think there are a variety of causes of pulmonary hypertension. We have seen what appeared to be primary arteriolar thickening. We have seen a number of cases similar to those described by Dr. Edwards with medial thickening and intimal proliferation. We have also seen a number of cases with multiple thrombi and recanalization.

Of the first three patients studied by Dr. Damman two presented such different clinical pictures that initially I could hardly believe they represented the same condition. One had a huge pulmonary artery with extraordinary calcification there and in the aorta, and the other had a relatively small heart. It is at least theoretically possible that in the former there was tremendous pulmonary blood flow with subsequent development of pulmonary hypertension and then reversal in the direction of the flow, whereas in the patient with the small heart the pulmonary hypertension may have been primary—we have no way of being sure.

Dr. Adams raised a question that is very real, that we have debated back and forth. We too have seen a number of young infants—most of them with balanced electrocardiograms and a few with right axis deviation—who had pulmonary hypertension and a large ductus and had been greatly helped by ligation. Certainly all of our patients with a large ductus who have had catheterization have had evidence of tremendous left-to-right shunt and a small right-to-left shunt. I think Dr. Adams is right in saying that pulmonary hypertension is the most serious thing; I appreciate that very much.

I am sure that in patients with severe pulmonary hypertension there is no evidence of a left-to-right shunt and there is a marked right-to-left shunt. In a number of cases there may be a neurogenic factor causing pulmonary hypertension; in others there may be some difficulty in opening up the pulmonary vascular bed. Pulmonary hypertension is one of the interesting new fields. I certainly cannot begin to answer all the questions—we are only at the beginning of our studies.

As to the question of the cause of dyspnea, it is caused by lack of an adequate supply of oxygen. With pulmonary stenosis and no shunt at all, it is just that little blood gets to the lungs. Furthermore, these patients are unable to increase their pulmonary blood flow with exercise, as the normal person does. Consequently dyspnea brings them up short but there is no marked fall in the arterial oxygen saturation. In patients with a tetralogy of Fallot the existence of a shunt means that not only is there no increase in the circulation to the lungs with exercise but there is a definite increase in the volume of venous blood shunted into the systemic circulation; consequently there is a marked fall in the oxygen saturation as well as in subjective dyspnea.

As to closure of the ductus arteriosus, we have discussed that often. It is remarkable to me that two of our patients have lived to 21 and 20 years of age and have done as well as they have. We did try corticotropin (ACTH) on one or two infants and got nowhere. Then, as I came to believe that there were congenital anomalies in the lungs, the use of corticotropin seemed futile.

We have hesitated to put in a ductus, because at most it would only relieve the strain on the heart and not alter the fundamental condition.

Metabolic Effects of Folic Acid Antagonists in Acute Leukemia. Dr. Harry A. Waisman, Ph.D. (by invitation), Dr. Julius B. Richmond (by invitation), and Dr. Henry G. Poncer, Chicago.

The temporary remission obtained in acute leukemia with folic acid antagonist therapy had been encouraging enough so that a study on the influence of the metabolic analogues on this disease process was desirable. It is becoming increasingly apparent that the folic acid antagonists are in all probability more important as citrovorum factor antagonists. Observations on children with leukemia have shown that citrovorum factor overcomes mouth lesions caused by aminopterin. In further investigation of the role of citrovorum factor, laboratory experiments showed that this newer vitamin is more effective than folic acid in counteracting the aminopterin. Since citrovorum factor is related to enzymes concerned with nucleic acid synthesis, metabolic studies were done on leukemic patients before and during antagonist therapy. Urinary excretion of citrovorum factor by leukemia patients was compared with that of normal individuals. The citrovorum content of tissues from these patients were analyzed post mortem and compared with normal tissues of children who died of other diseases unrelated to liver pathology.

Disordered protein and nucleoprotein synthesis associated with defective cellular maturation of bone marrow of leukemic patients was investigated by studies of blood levels of amino acids. It was found that methionine, valine, and phenylalanine were higher in leukemic children, but the values did not return to normal after "aminopterin" (4-aminopteroylglutamic acid) therapy. The relationship of skin hyperpigmentation to tyrosine and phenylalanine metabolism during treatment was investigated.

DISCUSSION

Dr. Sidney Farber, Boston: I should like to express my appreciation for Dr. Waisman's excellent presentation and for the work of his group. Research of this kind is badly needed to explain the still fundamental problem of the nature of the leukemic process. My colleagues and I have been much interested in the citrovorum factor. Work in a number of different laboratories in this country would certainly support the opinion expressed by Dr. Waisman concerning the essential importance of this factor in the synthesis of nucleoproteins.

The folic acid antagonists were so named because of their action on the growth of bacteria under special conditions. It is of great interest that they were of importance in leukemia but of no essential importance to understanding of the leukemic process. We pointed out soon after our demonstration that folic acid antagonists were effective in producing remissions.

Dr. Waisman may be interested in the observation made by two of my younger colleagues, both working with others of our group, in respect to synthesis of the citrovorum factor from folic acid. Dr. E. J. Modest was able some two years ago to synthesize a new chemical, a dihydrotriazine, which is effective in inhibiting the synthesis of citrovorum factor from folic acid, but in a manner quite different from that utilized by the anti-folic-acid compounds, such as "aminopterin," in coming to the same end-result.

If we take Dr. Waisman's clear diagram showing the synthesis of nucleoproteins, beginning with folic acid, and draw two lines, one on each side, one illustrating the process of formylation and the other that of reduction, we can illustrate the difference in action of these two totally unrelated types of chemical compounds, the dihydrotriazines and the folic acid antagonists, in interrupting the mechanism. We have here a tool which will lead us to further understanding of the leukemic process. It is interesting that this new chemical (the dihydrotriazine) is effective in leukemia in the mouse. We do not have information yet on its effect upon the leukemia process in man.

Dr. Harry A. Waisman, Chicago: I am certainly grateful to Dr. Farber for his comments. I am pleased to know that we have further compounds which will interfere with abnormal processes. Compounds such as those Dr. Farber described will account for much of the progress we will make in this field.

Of course the role of citrovorum factor has now been slightly more clarified. When it was first synthesized by the Lederle group the formula was not distinctly known. Now I think we must recognize that the synthetic material is in two different forms, if you will, D and L. The L form is more effective. So-called folinic acid is the natural form, and the citrovorum factor, or leucovorin, as described by the Lederle group, is the synthetic form.

One other point I should like to mention because "Aminopterin" is toxic to some patients. (We do not know why individual differences occur in degree of the toxicity.) One can give "Aminopterin" early in the morning by mouth and six hours later follow it with an injection of citrovorum factor and avoid the toxic mouth lesions. In other words, one can get the effect for six hours and then counteract the amount of antagonist which is absorbed but not yet detoxified or excreted.

With regard to the other question, the adult patient with acute leukemia definitely showed a clinical remission, but unfortunately her bone marrow did not respond. She was so improved that she was able to go home. She lived for two months on low doses of "aminopterin" and then had a sudden accident which was unexplained, since she died outside the hospital. She was 65 years old.

A Lipid Metabolic Disorder—Disseminated "Lipogranulomatosis"—A Syndrome with Similarity to, and Important Difference from, Niemann-Pick and Hand-Schüller-Christian Disease. DR. SIDNEY FARBER, Boston.

In 1947 (in a Mayo Foundation lecture) I described the finding of what appeared to be a lipid metabolic disorder with granulomatosis components, reminiscent of Hand-Schüller-Christian disease with histological changes suggestive but not typical of Niemann-Pick disease, in a 14-month-old girl. The simplified term "lipogranulomatosis" was employed for convenience.

Two later cases, this time in siblings (a girl who lived for 13 months and a boy who lived to 9 months of age), have shown striking similarity clinically and pathologically to the first case, and have led to chemical studies of the organs and tissues. The disease is recognizable at birth or shortly after and is characterized by a hoarse cry, feeding difficulties, symptoms of respiratory difficulty, and a course marked by such extensive involvement of the joints and periarticular tissues that a diagnosis of rheumatoid arthritis has been made by workers in that field on clinical examination alone. Moderate enlargement of the liver, pigmentation of the skin, development of subcutaneous nodules with increasing joint involvement, and destruction, erosion, or loss of substance in bones, including the clavicles, the ulna, and the proximal metaphases of the tibia, are further important findings.

Postmortem examination revealed a picture strikingly similar in all three patients. There was widespread involvement of the pleura, the pericardium, the synovial lining of the joints, periarticular tissues, the liver, the spleen, lymph nodes, the alveolar walls and the alveolar spaces, the gall-bladder, and the nerve cells of the brain, the spinal cord, and the ganglions. The essential features of the pathological processes were two:

Infiltration and replacement of the normal architecture of these organs and tissues by foam cells which stained moderately well with the modified myelin sheath stain of Smith-Dietrich for sphingomyelin and a diffuse mild granulomatous reaction in many of the involved areas, particularly around joints and serous surfaces. The changes in the brain were reminiscent of those in Tay-Sachs disease and Niemann-Pick disease but differed in certain important respects.

Chemical studies were made by Dr. L. Lahut Uzman. He noted an over-all increase in the total lipid content of the spleen, heart, liver, and lungs. Partition of the lipid in a ternary solvent mixture consisting of chloroform, methanol, and water resulted in the accumulation of a fraction at the chloroform-methanol, methanol-water interphase. This was collected, purified, and analyzed. It proved to be insoluble in chloroform and water but soluble in a chloroform-methanol mixture containing less than 5% water, and consisted of 33% carbohydrate (glucose equivalents), 24% lipid, and 43% protein or polypeptide. The lipid moiety appeared to be composed of a mixture of fatty acids, neutral triglycerides, and phosphatides, with the greater part of the phosphatide moiety consisting of unsaponifiable phosphatide (presumably sphingomyelin).

The findings in these three cases appear definite enough to characterize a congenital disorder of lipid metabolism which may be differentiated clinically, pathologically, and chemically from Niemann-Pick disease, to which it is most closely related, and also from Hand-Schüller-Christian disease (Letterer-Siwe's disease), with which it has elements of similarity. This disease may prove to be a bridge between those such as Niemann-Pick and Gaucher's disease,

which appear to be true disturbances of intracellular lipid metabolism, and those such as Hand-Schüller-Christian disease, which are granulomatous and apparently not primary disturbances of metabolism.

DISCUSSION

DR. IRVING J. WOLMAN, Philadelphia: This is a remarkable series of cases. Would one expect a bone marrow aspiration in a patient of this sort to yield the characteristic cell?

DR. SIDNEY FARBER, Boston: I should have stressed the fact that the bone marrow is involved and that if one does a bone marrow biopsy one stands a good chance of finding the characteristic cells. If one finds them one should also stand a good chance of making a diagnosis of Niemann-Pick disease.

The clinical picture I described may be found to be typical for these 3 cases and may not be encountered in the next 20 or 30. We should, with a disease of this kind, expect to see a number of unrelated clinical pictures in the future.

PAPERS READ BY TITLE

Experimental Production of Eosinophilia by a Host-Foreign Larval Nematode. DR. MARGARET H. D. SMITH (by invitation), and DR. PAUL C. BEAVER (by invitation), New Orleans.

Recent clinical reports (reviewed by Beaver and co-workers, *J. Pediat.* **9**:7 [Jan.] 1952) suggest that the clinical picture of eosinophilia associated with hepatomegaly, and sometimes with pulmonary infiltrations, tumorous masses in the eye, and so on, is probably due to infection with a parasite not well-adapted to the human host. In order to lend experimental support to these clinical observations, the following investigation was undertaken.

Two mentally defective children shown to be free of intestinal parasites were infected with ova of Toxocara canis (the dog ascaris) and carefully followed for many months. Each received 200 ova, administered in one case by feeding and in the other by stomach tube. The infectivity of these eggs was demonstrated by administering 200 ova of the same batch to each of two mice; three months and seven months later, respectively, 60 and 64 active larvae were recovered from the two mice.

The first subject was a 2-year-old Negro girl with decerebrate rigidity as a result of meningitis. She was known to have had human-type ascariasis but had been free of ova for at least a month. During the three weeks following infection with dog ascaris ova, her temperature rose to 100 F. rectally on five different days, but there was never any hepatomegaly, pulmonary infiltration, or other manifestation of ill health. Her eosinophilia, which had ranged between 0 and 3%, rose within one month to 44 to 52% of the total leucocyte count and fell thereafter to 20 to 30%. Thirteen months after infection the eosinophiles represented 15 to 16% of the total leucocytes.

The second child, a severely retarded child with minimal mediastinal tuberculosis, was 3 years of age at the time the ascaris ova were administered. The edge of her liver became just palpable during the ensuing month, but the child ate and gained as usual. Neither fever nor pulmonary infiltration was detected. The eosinophiles, which prior to infection represented 3 to 6% of her total leucocyte count, rose within one month to 8% and by the end of three months to 40 to 45%. They fluctuated between 34 and 80% for seven months, subsiding only slightly at the end of one year. Two courses of "hetrazan" administered to this child resulted each time in a noticeable rise in the eosinophile count within a few days, followed by a fall and then a return to the pretreatment level.

Stools of both patients were examined repeatedly after infection but no ova were ever found. Spinal fluid findings were always within normal limits, nor were any bone or sense organ lesions detectable on x-ray examination or otherwise.

To summarize: Observations on two children infected with dog ascaris showed that a long-lasting eosinophilia can follow infection with a host-foreign parasite and that such an infection may be asymptomatic. They suggest that a host previously infected with a parasite may show a prompter rise in eosinophiles; that a relatively small dose of the infective agent (as used here) produces eosinophilia without systemic manifestations; and that "hetrazan" cannot be counted on to clear up the eosinophilia.

A Proposed Basis for Comparing the Incidence of Retrolental Fibroplasia in Different Nurseries. Dr. William Silverman (by invitation) and Dr. Richard Day, New York.

Numerous reports have been published indicating wide variations in the geographic and temporal incidence of retrolental fibroplasia. With few exceptions these reports have failed to indicate sufficiently clearly the frequency distributions of the birth weights of the infants. Since the incidence of the disease rises sharply in the lower weight groups, slight differences in the numbers of small infants can result in large differences in incidence. The importance of the period of gestation in addition to weight has also been recently reported by Schlesinger. Analysis of 80 cases occurring among 257 surviving infants in one hospital (Babies Hospital) demonstrates the difficulty of drawing conclusions in the absence of comparable groups in which the same criteria and categories have been used.

It is suggested that more uniform criteria of diagnosis and techniques and frequency of ophthalmoscopic examination be adopted by those reporting on retrolental fibroplasia. It would be desirable to record the following items of information for each infant whether affected or not and whether he survives or not. Data should be summarized in 100-gm. weight groups: (1) period of gestation in days, (2) birth weight, (3) any other measures of prematurity, (4) race, (5) sex, (6) dates examined, and (7) final ophthalmoscopic classification and age at which it was made.

Only when large groups described in this detailed way have been compared can a sure opinion be arrived at as to the variability of the disease or the effect of empirically designed regimens.

Irregularities of Postnatal Bone Maturation in Congenitally Malformed Children. Dr. H. P. G. Seckel (by invitation), Chicago.

Multiple-area x-ray studies of postnatal maturation of bones were done on a series of children born with localized or systemic anomalies of the skeleton. All patients had associated extraskeletal malformations. The diagnoses were: congenital hypoplasia of the hand skeleton, phocomelia with and without Fanconi's syndrome, congenital dislocation of the hip, arachnodactyly, mongolism, and primordial dwarfism with nanocephaly. Normal standards and standard deviations for skeletal maturation were compiled from four or five sources. Individual contralateral standards were used in unilateral disorders. (Slides were shown to illustrate the findings.)

From these studies it may be concluded that in or near an affected skeletal area (hand, elbow, shoulder, hip, knee, foot) the appearance of epiphyseal or carpotarsal ossification centers is either retarded or (rarely) accelerated or "disharmonic." The latter term refers to the presence of retarded and normal (to advanced) maturation in the same area. "Asymmetries" may be found in unilateral malformations. Bone ages can be estimated only in terms of "scatters."

These irregularities of skeletal maturation are considered "constitutional" in nature and may be "genetic" in a given case. An endocrine causation, especially hypothyroidism, seems excluded on purely clinical grounds in every instance and was expressly excluded by laboratory tests in the two patients with primordial dwarfism.

Study of I^{131} Uptake in Distinguishing Different Types and Degrees of Thyroid Deficiency. Dr. Samuel H. Silverman (by invitation), Dr. Claude J. Migeon (by invitation), Dr. John F. Crigler Jr. (by invitation), Dr. Robert Klein (by invitation), and Dr. Lawson Wilkins, Baltimore.

Slight modifications of the technique of studying the uptake of I^{131} have made it possible to determine when the thyroid gland is capable of taking up and retaining very small amounts of iodine. Studies have shown that in congenital cretins there are differences in the degree of athyreosis which correlate fairly well with either the severity of symptoms or the time of their appearance after birth. In patients with juvenile hypothyroidism who have not been treated there is usually a small but definite uptake of I^{131}. When these patients have previously been treated with thyroid usually no uptake can be detected. In tensive thyroid therapy may markedly decrease or abolish the uptake of iodine in patients who have no thyroid disorder. The administration of thyrotropic hormone restores the ability of the thyroid gland to take up iodine in patients who do not have thyroid disorders, but usually has no effect in patients with hypothyroidism.

The Emergency Maternity and Infant Care Program as Seen by Physicians Who Participated in It. Dr. Leona Baumgartner, and Dr. Myron Wegman, New York.

All physicians (a total of 5,575) who cared for emergency maternity and infant care patients in New York City were polled by questionnaire (three mailings) and telephone (a random sample) for their opinions on certain aspects of the program. A 50% response was secured, and since there was little difference in answers related to promptness or willingness to answer it is assumed that the sample is representative.

About 90% thought the program reached its objective. Slightly fewer, but still more than 75% of the total, were satisfied with the procedures of application and authorization and with the general administration of the program. More than 90% were satisfied with the method of payment directly to the physician and only a very small number, fewer than 1%, would have preferred a cash payment to the patient.

More than 90% of the physicians thought that the functioning of the plan had not interfered with the patient-physician relationship. Of the small numbers who thought the plan had produced a change, almost one-fifth thought it made the relationship better rather than worse. Pediatricians seemed more likely to think it better.

Availability of consultation services was generally appreciated, but there was not as much positive expression of approval for special nursing service as for medical consultation and services of visiting nurses.

The greatest dissatisfaction was in the amount of the fee paid, particularly the obstetric fee.

Two-thirds of the physicians did not respond to a question designed to give a general assessment of the program.

The opinions of pediatricians, obstetricians, and general practitioners were analyzed and the relationship to the number of cases the physician cared for. This analysis is thought to be unique in that it is apparently the only one recorded so far in which the opinions of all of the physicians who actually cared for emergency maternity and infant care patients in a community have been secured and analyzed.

The Prevention of Drowning. Dr. Harry F. Dietrich, Beverly Hills, Calif.

For the past 20 years approximately 7,000 persons in the United States have drowned each year. Drowning at ages 1 to 44 is the most common cause of nonvehicular accidental death. Drowning at ages under 15 causes as many deaths as are caused by cancer, tuberculosis, leukemia, or heart disease. Among all drownings, 10% occur in children under 5 years of age; 87% occur in males; and 50% result from the victim's being deposited in water by accident. These statistics raise questions that only emphasize our need for more detailed information in this field.

The general theory of accident prevention that embraces a reciprocal relationship between protection and education related to age is applicable to the problem of drowning. During the first two to three years more adequate protection is needed; with children aged 6 months to 3 years we must refrain from overemphasizing the virtues and minimizing the unpleasant properties of water; and after the child has "learned to swim" we must expand our educational efforts in relation to the child's interest in, and opportunity for, aquatic activity. Children must be taught that, while cramps, blows on the head, and hysterical swimming companions can rob them of their rather superficial ability to say afloat, knowledge of and respect for the properties of water will immunize them against drowning.

Genetic Aspects of Rheumatic Fever. Dr. May G. Wilson, Dr. Rose Lubschez (by invitation), and Dr. Nathan Epstein (by invitation), New York.

In a previous genetic and epidemiological study it was concluded that hereditary factors were primarily responsible for the familial concentration of rheumatic fever.

The data for analysis comprised findings on 112 families with 412 siblings selected because of the presence of at least one rheumatic child. It was postulated that the distribution of cases was consistent with recessive Mendelian inheritance.

For the past genetic analysis, families were selected from our adult cardiac follow-up clinic. The offspring of our adult cardiac patients as well as the children of their nonrheumatic brothers

and sisters were brought under medical supervision in a special pediatric clinic. The group now comprises 296 families and 619 children. The majority of the children have been followed from infancy for 10 to 15 years.

Genetic analysis of the data confirmed the fundamental importance of heredity in rheumatic fever. The argument as to the distribution of cases with specific hereditary mechanisms was considered, as was the possible nature of the inherent defect.

Frequency of Laboratory Evidence for Virus Pneumonia in Infants and Children. Dr. Robert Klein (by invitation), Dr. John W. Larson (by invitation), and Dr. Walter G. Dukstein (by invitation), Pittsburgh.

Various studies were performed on over 175 patients with respiratory illnesses who entered the Children's Hospital of Pittsburgh in the periods October, 1950 to May, 1951, and October, 1951, to March, 1952, in an attempt to establish the incidence of "virus" pneumonia.

Cold agglutinins, streptococcal MG agglutinins, and anti-Gallus agglutinins were determined on sera obtained as soon as possible after admission and 10 days to 2 weeks thereafter. In addition, attempts were made to culture viruses from nasal washings, blood, and autopsy material. Nasopharyngeal smears were examined for inclusion bodies. The usual bacteriological examinations, x-ray examinations, and blood counts were carried out.

The study was designed to include all cases of respiratory illness admitted to the hospital. A few unselected cases were missed, however, because of administrative problems or lack of enthusiasm in members of the house staff.

A clinical diagnosis was attempted from information obtained from the history and the course, including response to antibiotics. I examined many, but not a majority, of the patients.

The paucity of laboratory results suggesting virus pneumonia will be contrasted with the results of similar surveys among adult patients. Moreover, the few positive tests were in the older group of children. This observation suggests that either the "atypical" pneumonias of infancy are not produced by the same virus or by viruses at all or that the infant is unable to produce antibodies qualitatively or quantitatively similar to those of the adult in response to these viral infections.

Familial Autonomic Dysfunction with Defective Lacrimation. Dr. Conrad M. Riley (by invitation), New York.

In 1949 we reported in some detail five cases of what appeared to be a hitherto undescribed clinical entity under the title of "Central Autonomic Dysfunction with Defective Lacrimation." Since then, through the cooperation of other physicians and hospitals, we have accumulated a total of 33 well-documented cases. The increased size of the series now enables us to present a more definitive picture of the syndrome.

Certain features have been present in all cases in which the information was available. All patients were of Jewish extraction. All had defective lacrimation, excessive perspiration, abnormal drooling, emotional instability, general motor incoordination without specific neurological findings, and relative indifference to pain. In only one very young patient was there an absence of erythematous blotching of the skin of head and shoulders either during periods of emotional stress or while eating. In only one patient were the deep tendon reflexes reported to be normal; in all other cases they were either absent or markedly hypoactive.

Certain other features occurred frequently but were absent in an appreciable number of cases. Intermittent hypertension of marked degree which could be induced by excitement was found in all but 4 of the 28 cases in which the information was available. Frequent pulmonary infections and frequent unexplained fever were also common but not constant findings. Cyclic vomiting was a feature in almost two-thirds of the cases. The history of breath-holding spells in infancy and of bladder dysfunction (usually urinary frequency) was much more common than would have been expected in normal children. Electroencephalograms, when done, showed abnormalities in a high percentage of the patients observed. These abnormalities usually were suggestive of a convulsive disorder, but were not specific.

Other features occurred in these patients more frequently than would be expected in a normal sample, but their incidence was not high. Corneal ulceration, probably secondary to defective

lacrimation and corneal hypesthesia, had been present in almost one-third of the patients. Mental retardation was a problem in more than one-half of them. Convulsions had occurred in somewhat less than half.

In only a small fraction of the group was there any history which suggested central nervous system damage as an etiological factor. From a differential diagnostic point of view it is significant that five patients had undergone exploration for pheochromocytoma.

Of the 33 patients 10 have died, their deaths occurring at ages ranging from under 2 years to 17 years. The most frequent cause of death apparently was aspiration pneumonia. One child died in uremia, suggesting that intermittent hypertension had affected the kidneys. In nine autopsies lesions in the central nervous system were found twice. In one case there were multiple brain abscesses apparently secondary to aspiration pneumonia. In the other a small cyst was found in the thalamus. The patients still living range in age from about 1 year to 20 years. In the older patients there has been no real improvement in their general condition with the passage of time.

This condition has a familial incidence high in siblings but is not present in parents or collateral relatives. Among the 33 patients are 4 pairs of siblings. If the index cases which originally brought the family to the attention of a physician are excluded there remain among these families a total of 33 offspring. Of these, 11 have been afflicted with the same condition (4 cases well documented and 6 probable by history). This proportion is compatible with a Mendelian recessive characteristic.

In our experience the severity of the manifestations has varied tremendously in degree. It would seem highly probable that examples of the syndrome exist in which none of the incapacitating features is present. The affected children would probably be presented for examination because of behavior problems due to their emotional instability and motor incoordination.

Psychological Evaluation of Children with Cerebral Palsy and Its Implications in Treatment. ELSA MILLER, M.A. (by invitation), and DR. GEORGE B. ROSENFELD (by invitation), Buffalo.

Psychological evaluations of 330 children with cerebral palsy were analyzed, and the implications of the findings with regard to the treatment program were studied. The patients included all the children who had been under treatment or who had come to the Cerebral Palsy Diagnostic Clinic of the Children's Hospital within the five year period from Jan. 1, 1947, to Dec. 31, 1951.

Of the 330 children, 50% (164) had an IQ below 70, 22.5% (74) had an IQ between 70 and 89, 23% (77) had an IQ between 90 and 109, and 4.5% (15) had an IQ over 110. A further breakdown of the 164 mentally defective children shows that 45% had an IQ below 40. This intelligence distribution, with one-half the children mentally defective and three-fourths below average intelligence, is in sharp contrast with the usual concepts of intellectual capacity of children with cerebral palsy but agrees with the recent findings of Asher and Schonell in England.

While it is impossible with a certain percentage of such children to do a complete psychological examination, it has been found possible to get meaningful evaluations by allowing the child to use any method of response which he is capable of within his physical limitations. Reevaluation of these children after intervals ranging from 1 to 10 years corroborated the original findings.

During psychological examination, many specific problems are revealed, the knowledge of which has practical significance in treatment. Two of these problems, distractibility and visuomotor disturbances, were specifically studied and analyzed. All of the children 4 years of age or over (141) were studied for these factors. Forty per cent of the spastic children and 40 per cent of the athetoid were very distractible. However, only 8% of the athetoid in contrast to 39% of the spastic showed visuomotor disturbances.

Special disabilities such as distractibility and visuomotor defects, which can be best discovered on psychological examination, must be carefully taken into account by the physiotherapist, the occupational therapist, the speech therapist, and the schoolteacher. Teachers have to set up special techniques to help the distractible child direct his attention. More and shorter periods of therapy and schooling may be necessary.

It is becoming clear that the child's mental age as well as his neuromuscular condition and his chronological age are important in determining his capability of responding in various areas of treatment. Over 50% of our patients were seen first under 4 years of age. One-half of these were mentally defective. There is an increasing tendency at present to refer children for treatment when they are fairly young. A large number of these children are not yet capable of responding in many of the areas of treatment. Therapy may often be much more effective if postponed than if started too early. By evaluating the readiness of these children to respond in each area of treatment, we may meet the needs of more children more effectively with available facilities and personnel. By fitting the treatment to the psychological as well as to the neuromuscular status of the individual child, we will more frequently fulfill the aims of treatment and avoid the tremendous parental emotional turmoil which unsuccessful and perhaps unindicated treatment engenders.

With three-fourths of the patients below normal intelligence, one-half of the patients mentally defective, and a large fraction presenting specific disabilities, the aims of treatment for each child must be limited and defined in order to do the greatest good to the greatest number.

Analysis of Body Build. Part II: The Problem of Visualizing Differences in Bodily Proportions. Dr. Edith Boyd, Denver.

One obvious phenomenon of life is the progressive change in body form with age from the rotund infant with a relatively large head, a barrel-shaped trunk, narrow shoulders, and short legs to the elongated adult with a relatively small head, a flattened hour-glass-shaped trunk, and long legs. However, our knowledge of the variations in the patterns and timing of growth of the various regions has been insufficient for adequate evaluation of the progress of an individual child through this transformation. To visualize these changes in form, the series of yearly photographs of children being followed at the Child Research Council from birth through maturity were reduced to outline drawings held to the same height. The outlines were then arranged in order of various physical characteristics for each year and the individual child ranked according to position in the group at each age. Second, percentile standards were constructed of the central trend and variations in physical dimensions reduced to percent of height from data on the same group of children. When the photographic outline of a child at a given age and the percentile position of each of his dimensions on a rectilinear percentile standard are combined into one chart, the proportions of the individual child and their relation to those of the group can be seen at a glance. From a series of the combined charts, the individual child's age change in proportion can likewise be readily seen.

Clinical and Etiological Studies of an Outbreak of Herpangina in Philadelphia. Dr. L. P. Kravis (by invitation), Dr. K. Hummeler (by invitation), and Dr. M. M. Sigel (by invitation), Philadelphia.

This report of an outbreak of herpangina in Philadelphia during July and August of 1951 confirms Huebner's thesis that the Coxsackie group A viruses are the causative agents of this specific clinical entity.

Seventeen children ranging in age from 7 months to 11 years comprise the group of patients with typical throat lesions from whom Coxsackie group A virus was isolated. In four instances, there were multiple infections within the same household.

Virus of the same type as that recovered from their children was isolated from the stools of three asymptomatic mothers in the group, thus illustrating the fact that in apparent infections or silent carrier states do exist.

There was evidence suggestive of accidental infection of two children by a laboratory associate who worked with material heavily infected with Coxsackie virus and who carried virus in her stool.

Serological studies using the complement-fixation and neutralization techniques emphasized the causal relationship between Coxsackie viruses group A and herpangina. In the three cases which were tested, specific antibody titer rises were demonstrable, and in other instances in which only convalescent serum specimens were tested, high antibody titers were found.

Effects of Prolonged Multiple Transfusions on Hepatic Function and Structure. Dr. Carl H. Smith and (by invitation) Dr. Joan E. Morgenthau, and Dr. Irving Schulman, New York.

Studies were made on a group of children (all with severe Mediterranean anemia except one with sickle cell anemia) with hemosiderosis resulting from multiple frequent transfusions administered over a period of at least five years. To investigate the effects of iron overload on hepatic function and structure, complete liver function tests were performed on 18 of the children in 1947 and were repeated on 14 of these in the past year. Liver biopsies on five patients provided an opportunity to compare changes with those found in hemochromatosis and to correlate if possible functional and structural changes. Elevated levels of serum iron and 100% saturation of the iron-binding protein characterized each of these patients.

The ages in 1947 ranged from 2 to 10 years and all subjects had been receiving transfusions since early infancy. The tests included cephalin flocculation, sulfobromophthalein sodium retention, cholesterol and esters, serum bilirubin, total protein, and albumin-globulin ratio. At this time (1947) the only abnormalities found consisted of slightly elevated sulfobromophthalein retention in two of the patients, both 10 years of age. In 1951, these studies, with the addition of thymol turbidity, alkaline phosphatase, and icterus index, were repeated on 14 of the original patients. In this group, definitely abnormal sulfobromophthalein retention was found in eight patients and, significantly, all were over 10 years of age. The two children who had abnormal function in 1947 showed progressive dysfunction in the four-year interval as evidenced by sulfobromophthalein retention twice the original magnitude. No abnormalities were found in any of the other laboratory tests.

These studies suggest that liver function may be impaired in children who have been subjected to iron overload for long periods. The appearance of impairment seems to be a function of time, no children having demonstrated abnormalities under the age of 10 years. Evidence in two cases suggests that the impairment may be progressive.

Liver biopsies were performed in five of the patients. Two patients were over 10 years of age, and three were 5 to 8 years old. All biopsies revealed tremendous hemosiderin deposition in the parenchymal cells, in the Kupffer cells, and in giant cells at the periphery of the lobules. Two of the patients had definite increase in periportal fibrous tissue. There was no correlation between the pathological appearance of the liver sections and the liver function studies.

Angiography in a Case of Hydranencephaly. Dr. H. E. Thelander and Dr. E. B. Shaw, San Francisco.

This paper is an analysis of a case of hydranencephaly. The diagnosis was made by transillumination, pneumoencephalography, angiography, and postmortem findings. The lack of brain tissue, even in the cerebellum, was revealed very nicely by pneumoencephalograms taken with the child turned head down. The angiography of the brain revealed many points of interest, and it is believed this is the first case of hydranencephaly studied by this method. Examination of the brain tissue revealed small cavities which were lined with ependymal cells, and it is our concept that in this case the secretion of spinal fluid in these cavities expanded and destroyed the brain tissue completely. In other words, in this case hydranencephaly actually was an extreme case of porencephaly.

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Abstracts from Current Literature

Biochemistry; Bacteriology and Pathology

LYOPHILE CONVALESCENT SERA. JULIO C. BELTRAN, Arch. pediat. Uruguay **22**:816 (Nov.-Dec.) 1951.

The author emphasizes the importance of convalescent sera in the prophylaxis and treatment of infectious diseases. He presents the advantages of availability of a stock of convalescent sera of a variety of diseases to be used at the right moment. He draws attention to the rapid deterioration of sera preserved in the liquid state and to the practical difficulties of storage and transport in the frozen state, in contrast to the excellence of preservation in the dry state, especially when desiccation is made by the process of lyophilization.

After describing the method of lyophile drying used in the "Central de Sangre y Plasma" of the Faculty of Medicine of Montevideo, the author considers the properties of lyophile convalescent sera. He reports on the results obained with the use of such sera in the case of infants and adults, noting particularly their therapeutic activity and the absence of untoward effects. In conclusion, he points out the necessity of instituting in Uruguay a convalescent serum center similar to the centers found in other countries.

FROM THE AUTHOR'S SUMMARY.

Metabolism; Infant Feeding; Milk and Other Foods

EFFECT OF HEAT TREATMENT ON THE NUTRITIVE VALUE OF MILK PROTEINS: IV. BIOLOGICAL VALUE OF UNHEATED AND AUTOCLAVED DRIED SKIM MILK. ROSE ALLEN KRAFT and AGNES FAY MORGAN, J. Nutrition **45**:567 (Dec. 10) 1951.

The greater sensitivity of milk proteins to autoclaving than to dry heating is shown by the experiments of Kraft and Morgan. Autoclaving at 118 or 120 C. for 15 minutes appeared to destroy from one-half to two-thirds of the biological value of these skim milk proteins, and autoclaving for 25 minutes left the product without growth value for rats. Dry heating at these temperatures for longer periods than these has been shown to produce significant but much less marked changes in casein and lactalbumin. The changes produced appeared to involve chiefly loss of lysine, since addition of 1% lysine, either alone or with equal amounts of valine and methionine, improved the diets markedly, while similar additions of valine or methionine alone were without effect.

FREDEEN, Kansas City, Mo.

FORTIFICATION OF BREAD WITH LYSINE: I. LOSS OF LYSINE DURING BAKING. HANS R. ROSENBERG and EDWARD L. ROHDENBURG, J. Nutrition **45**:593 (Dec. 10) 1951.

The loss of lysine in bread due to baking was found to be about 15% by microbiological assay. The loss varied from 9.5 to 23.8%. Toasting a slice of bread reduced the lysine content by 5 to 10%. A similar loss occurred when bread became stale and dry.

FREDEEN, Kansas City, Mo.

BIOLOGICAL AVAILABILITY OF CERTAIN FOODS AS SOURCES OF RIBOFLAVIN. GLADYS EVERSON, ELINOR PEARSON, and ROBERTHA MATTESON, J. Nutrition **46**:45 (Jan. 10) 1952.

Metabolism studies have been conducted on four young women to determine the degree to which green peas, ice cream, almonds, and soy beans are digested by this age group. The data revealed excellent digestion of ice cream and less satisfactory digestion of the other test foods. A larger proportion of riboflavin furnished from ice cream was available for use than was available from the two types of legumes or almonds.

FREDEEN, Kansas City, Mo.

A Study of the Minimum Calcium Requirements of Adult Men. D. M. Hegsted, Irma Moscoso, and Carlos Collazos Ch., J. Nutrition **46**:181 (Feb. 11) 1952.

The minimum calcium requirement of men is probably so low that deficiency is unlikely on most natural diets. When calcium supplies are limited, little effort should be made to increase the consumption of calcium by men. Available calcium should be reserved for children and women in the childbearing age.

Fredeen, Kansas City, Mo.

Retention of Crystalline Vitamin B_{12} by Healthy Male Individuals Following Intramuscular Injection. Calvin Lang, Robert A. Harte, C. L. Conley, and Bacon F. Chow, J. Nutrition **46**:215 (Feb. 11) 1952.

The authors' results demonstrate the ability of healthy males to retain quantities of vitamin B_{12} after a single intramuscular administration, amounts presumably many times larger than those estimated to be present in normal diets. The normal subjects used in these experiments were not saturated with vitamin B_{12}, in spite of a presumably adequate intake of food.

Fredeen, Kansas City, Mo.

Nutrition Resurvey in Bataan, Philippines, 1950. Helen B. Burch, Juan Salcedo Jr., Eufronio O. Carrasco, and Carmen L. Intengan, J. Nutrition **46**:239 (Feb. 11) 1952.

A nutritional resurvey by microchemical methods and a dietary and clinical study have been made in Bataan on 200 persons. Sixty-four per cent of these were examined in both 1948 and 1950. The marked increases in blood and urinary thiamine and in hemoglobin indicate a major change in the intake of thiamine and iron in the diet. The results of the dietary study are, for the most part, in accord with the chemical findings. They also point toward satisfactory intakes of thiamine and iron and toward lack of ascorbic acid and riboflavin. They reveal a critical lack of calcium. The chemical findings on changes in thiamine levels and in hemoglobin concur with the clinical reports on the improvement in health of the people following the inauguration of the enriched rice program in Bataan.

Fredeen, Kansas City, Mo.

Growth and Development of Infants Receiving a Proprietary Preparation of Evaporated Milk with Dextri-Maltose and Vitamin D. Loraine H. Frost and Robert L. Jackson, J. Pediat. **39**:585 (Nov.) 1952.

Infants fed "lactum" with supplements of vitamins and the usual addition of solid foods grow and develop as well as or better than the average infant does.

Macdonald, Pittsburgh.

Nutrition and Health Study of Bantu Boys, South Africa. H. le Riche and others; South African M. A. J. **26**:207 (March 15) 1952.

This is the first in a series of papers describing studies of a group of Bantu boys. The study is too detailed and extensive to permit abstracting. It was done by a team of 12 associated scientists and involved clinical and dental examinations, check x-rays, stool and urine examinations, determinations of hemoglobin and packed cell volume, and tuberculin and Schick tests.

McGuigan, Evanston, Ill.

Nutritional Disturbances in the Infant and Small Child. M. Bose, Indian J. Pediat. **18**:145 (Oct.) 1951.

The author discusses briefly the nutritional requirements of infancy and childhood, with descriptions of the commoner nutritional disturbances and their treatment.

McGuigan, Evanston, Ill.

Investigation Concerning the Mechanism of the Action of Nestargel (Carob Meal). Par Chr. Rivier, Schweiz. med. Wchnschr. **82**:256 (March 8) 1952.

The passage of food through the stomach and intestinal tract of infants is not modified by the addition of carob meal. Aerophagy is diminished, and the consistence of a meal containing

carob meal is little modified in the stomach. The viscosity of the stomach contents is maintained. Neither ptyalin nor pepsin nor the pH of the infant's gastric juice diminishes the viscosity of a meal containing carob meal. Such a diminution is due solely to dilution by the digestive juices.

AMBERG, Rochester, Minn.

TRANSMISSION OF FLUORINE THROUGH PLACENTA AND MAMMILLARY GLAND. H. R. HELD, Schweiz. med. Wchnschr. **82**:*297* (March *22*) 1952.

Fluorine passes through the placenta and is transmitted to the breast milk. The fluorine content of the cord blood corresponds, as a rule, to that of the maternal blood; that of the milk is considerably less. On administration of sodium fluoride, the fluorine content of the blood of the mother and that of the milk can be increased, but the relative increase in the milk is much less than in the blood.

AMBERG, Rochester, Minn.

THE POTASSEMIA CURVE AS AFFECTED BY THE GIVING OF POTASSIUM CHLORIDE, ALONE AND WITH EITHER DESOXYCORTICOSTERONE, ADRENALIN, OR SODIUM BICARBONATE. G. M. DORE, Minerva pediat. **4**:18 (Jan.) 1952.

In children, desoxycorticosterone, epinephrine, and sodium bicarbonate were each found to have a strong action in depressing the content of potassium in the blood when given with measured amounts of potassium chloride. These findings are similar to those which have been reported for adults.

HIGGINS, Boston.

THE EFFECTS OF EXPERIMENTAL ALKALOSIS ON THE ELECTROLYTIC EQUILIBRIUM OF THE NORMAL CHILD. G. CORDA, Minerva Pediat. **4**:21 (Jan. 15) 1952.

Ten to fifteen gm. of sodium bicarbonate daily was given to children over a period of seven days. Chemical studies of the blood and urine indicated that there had been some intracellular replacement of potassium by sodium, occasional withdrawal of chlorine from the tissues, and a definite diuresis.

HIGGINS, Boston.

LACTOFLAVIN AND CARBOHYDRATE METABOLISM. SEVERINO PEDONE, Riv. clin. pediat. **49**:251 (April) 1951.

The author brings our attention to the fact that riboflavin (lactoflavin) in a 1-mg. dose has an inconsistent action, depending on the subject's neurovegetative constitution. In the double dose of 2 mg. it has a constant and modest hyperglycemic action even in those cases in which with a 1-mg. dose a slight hypoglycemic action was apparent. Moreover, it has a certain potentializing effect on hyperglycemia both from a charge of glucose and from epinephrine; it has a moderating action on hypoglycemia from insulin. When riboflavin is associated with desoxycorticosterone and insulin, it has a more moderating effect than the one obtained with riboflavin plus insulin. Through the experiments carried out and the results obtained, the author holds to the hypothesis that riboflavin may have an action similar to that produced by epinephrine, presumably stimulating, as it does, the vegetative sympathetic nervous system centers, inasmuch as through the action of the adrenal cortex, riboflavin is transformed from provitamin into vitamin.

FROM THE AUTHOR'S SUMMARY.

REASONS FOR DISCONTINUANCE OF BREAST FEEDING IN INFANTS OF LOW SOCIOECONOMIC LEVEL, AGED LESS THAN 4 MONTHS. ANTONO STABILE and CARLOS A. BAUZE, Arch. pediat. Uruguay **23**:30 (Jan.) 1952.

The analysis of the reasons in 421 cases showed these to be the important ones: absence of or low supply of breast milk, 77.9%; inability to suck, 9.2%, and mastitis and allied conditions, 3.3%. Some suggestions are made to decrease negative factors.

FROM THE AUTHORS' SUMMARY.

INFLUENCE OF POOR NUTRITION UPON THE FAT CONTENTS OF BREAST MILK. H. HÜLLER-STEPHANN, Ztschr. Kinderh. **67**:495, 1950.

Determination of the fat content of the breast milk of 116 mothers showed an average value of 2.91%. The specimens were taken from the mixed 24-hour yield of milk from mothers who regularly supplied breast milk centers or whose children were patients at the hospital.

Examinations by other authors of breast milk of women in good nutritional status have indicated an average value of 4.01%. Statistical analysis shows that aside from the large number of specimens showing values around 3% there is a significant reduction in the fat content of the milk in 10% of the women (below 2%). It was also observed that low fat values occurred more frequently in the milk of women whose total milk production was low and that the fat content of the milk of good producers was usually high. The author attributes the low fat content of the breast milk to the poor nutritional state of the mothers.

GLASER, Jerusalem.

AMINO ACID CONTENT IN THE BLOOD OF THE UMBILICAL CORD. K. SCHREIER and H. Stieg, Ztschr. Kinderh. **68**:563 (No. 6) 1950.

Analysis of samples of blood from the umbilical cords of thirteen newborn infants has shown that the essential amino acids are present in higher concentration than in the blood of newborns or adults. The blood level of the various amino acids is not equally elevated, a fact from which the authors feel that one could draw conclusions as to the significance of various amino acids for the metabolism of the fetus.

GLASER, Jerusalem.

IRON METABOLISM IN INFANTS. Y. M. FEUILLEN and M. PLUMIER, Acta paediat. **41**:138 (March) 1952.

In this first part of their investigations on iron and metabolism in infants, the authors have estimated the iron in breast milk, cow's milk, and different diets most frequently employed in pediatric clinics. They conclude that infants fed artificially often ingest three to four times more iron than breast-fed infants of the same age and that anemia in the former is not due to the lack of iron in their diet.

FROM THE AUTHORS' SUMMARY.

Vitamins; Avitaminoses

VITAMIN B_{12} AND THE PRODUCTION OF POLYCYTHEMIA BY COBALT. STANLEY LEVEY and JAMES M. ORTEN, J. Nutrition **45**:487 (Dec. 10) 1951.

Levey and Orten concluded from their data that cobalt does not produce polycythemia by way of the intermediary formation of vitamin B_{12}.

FREDEEN, Kansas City, Mo.

TOTAL PLASMA PROTEIN AND PLASMA FIBRINOGEN IN ASCORBIC ACID DEFICIENCY AND IN SCURVY IN THE MONKEY. R. J. SALMON and C. D. MAY, J. Nutrition **46**:515 (April 10) 1952.

In monkeys the total plasma protein did not appear to be altered in scurvy more than would be attributable to malnutrition, but the plasma fibrinogen was considerably elevated. Secondary deficiencies of folic acid, colinic acid, or vitamin B_{12} cannot be held responsible. Adrenalectomy did not affect the level of plasma fibrinogen and did not prevent its rise when the monkey was made scorbutic. Thus it seems probable that ascorbic acid plays a role in the production of plasma fibrinogen separate from any effects of impaired liver function or hemorrhage.

FREDEEN, Kansas City, Mo.

Hygiene; Growth and Nutrition; Public Health

CHILDHOOD MORTALITY FROM ACCIDENTS. A. B. ROSENFIELD, Minnesota Med. **35**:424 (May) 1952.

Twenty per cent of the 1,804 accidental deaths in Minnesota in 1951 were those of persons less than 20 years of age. Between the ages of 1 and 19 years, accidental deaths constituted

38.5% of all the deaths in this age group. Motor vehicle fatalities were responsible for 36% of all the accidental deaths in childhood. Drownings were responsible for 18% and burns for 10%, with fatalities due to firearms in fourth place. Under one year of age, suffocation was given as the leading cause of accidental death.

STOESSER, Minneapolis, Minn.

MORTALITY IN YOUNG CHILDREN IN THE CITY OF ABERDEEN DURING THE FIFTY YEARS 1900-1949. JOHN CRAIG, Arch. Dis. Childhood **26**:409 (Oct.) 1951.

The deaths in young children in the second, third, fourth, and fifth years of life in the City of Aberdeen, Scotland, during the 50-year period from 1900 to 1949 inclusive have been studied.

There has been a striking fall in the total deaths, due largely to lowered mortality from measles, whooping cough, pneumonia, and tuberculosis. Diphtheria is no longer a common cause of death; indeed, the disease has almost disappeared. Scarlet fever is at present a mild disease. So great has been the fall in the mortality of the infectious diseases that in 1949 there was not a single death among young children in Aberdeen from measles, whooping cough, scarlet fever, or diphtheria.

Deaths from tuberculosis are now due mainly to meningitis, the end-result of a primary lung infection, and deaths from abdominal tuberculosis are so rare that there was only one in the last 11 years of the half-century.

A persistently common cause of death was pneumonia. Its mortality fell steadily throughout the 50 years but more quickly in the last six years, when it has caused few deaths.

Accidents continue to be a relatively common cause of death of young children, and at present they head the causes, along with pneumonia and tuberculosis. Fewer deaths are now caused by burns and scalds, and the mortal accidents are due to motor vehicles and drowning.

KELLY, Milwaukee.

DEATH DUE TO ACCIDENTS IN CHILDHOOD, ESPECIALLY DEATH DUE TO STREET TRAFFIC. J. DETTLING, Schweiz. med. Wchnschr. **82**:377 (April 12) 1952.

The incidence of violent death of children is considered in detail, with special attention to death charged to motor vehicles. The necessity for instruction in traffic hazards in all schools is emphasized. Children should not play in streets. The need of special places for play is stressed.

AMBERG, Rochester, Minn.

Prematurity and Congenital Deformities

NEUROLOGIC COMPLICATIONS ASSOCIATED WITH HEREDITARY DEFORMING CHONDRODYSPLASIA. A. SLEPIAN and W. B. HAMBY, J. Neurosurg. **8**:529 (Sept.) 1951.

Hereditary deforming chondrodysplasia is described as a congenital abnormality of osteochondral development, causing irregularity and arrest in growth at the metaphyseal ends of long bones, with resulting deformity and the occurrence of multiple cartilaginous masses, which, with calcification, become osteocartilaginous.

Neurologic complications of this disease are rare. Approximately 1,000 cases of hereditary deforming chondrodysplasia have been reported, in only 19 of which were neurologic complications found. The authors report 2 new cases of such complications in brothers, making a total of 21.

In their first patient an exostosis of the cervical vertebrae compressed the spinal cord; in the second an exostosis of the femur compressed the sciatic nerve. Two children of the second patient also bear uncomplicated stigmata of the disease.

In the literature males were involved in 14 of 15 reported cases in which the sex was mentioned. The spinal cord was involved in 10 cases; the sciatic nerve, in 6; the peroneal nerve, in 2, and the brachial plexus and ulnar nerve, in 1 case each.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.]

TWO ATYPICAL CASES OF CHONDRODYSPLASIA. J. W. C. DE GROOT, J. Pediat. **39**:715 (Dec.) 1951.

De Groot reports two unusual cases. The first is a case of a chondrodystrophy in a newborn infant with partial arachnodactyly. The second is a case of a mixture of chondrodysplasia and gargoylism.

MACDONALD, Pittsburgh.

ADRENOCORTICOTROPHIC HORMONE IN THE THERAPY OF RETROLENTAL FIBROPLASIA. J. T. LANMAN, L. P. GUY, and J. DANCIS, Pediatrics **9**:27 (Jan.) 1952.

Five premature infants in whom retrolental fibroplasia was thought to be developing were treated with corticotropin (ACTH). Therapy began between the 7th and 37th day of life and was given for from 30 to 66 days. The usual dose ranged from 20 to 40 mg. every 24 hours, divided into four intramuscular doses. In the treated infants there developed a rise in the urinary formaldehydogenic steroid output, a reduction in circulating eosinophiles, cutaneous pigmentation, rounding of the face, transient and usually minimal edema, and hyperglycemia and glycosuria. One infant died during therapy with a hyperchloremic acidosis, hyperkalemia, and Pseudomonas aeruginosa septicemia. In the four surviving infants retrolental fibroplasia progressed to extensive cicatrix formation behind the lens. Corticotropin, as employed in this study, was an ineffective therapeutic agent.

FROM THE AUTHORS' SUMMARY.

ETIOLOGY OF CONGENITAL ANOMALIES DEVELOPED IN THE COURSE OF PREGNANCY. CAUSSADE, NEIMANN, and GINSBOURGER, Pédiatrie **39**:567 (No. 5) 1950.

Aside from hereditary factors, environmental factors active during pregnancy have been considered with ever-increasing interest as causes of congenital malformations. These factors may cause real malformations or arrest development. The various factors are defective implantation, insufficient maternal diet, infections, intoxications (accidental or due to certain drugs), endocrine disturbances, trauma, and roentgen or radium rays. The discovery of these environmental causes of malformations point the way toward preventive measures during pregnancy and give rise to optimism for the normal development of further offspring in families where a malformation has occurred.

GLASER, Jerusalem.

ETIOLOGY OF RETROLENTAL FIBROPLASIA. H. GOLDMANN and W. TOBLER, Schweiz. med. Wchnschr. **82**:381 (April 12) 1952.

In the case of retrolental fibroplasia, reported here, the patient had a birth weight of 1,100 gm. and was placed in an incubator when 30 hours old. It was kept in the incubator for 52 days. For 24 days the concentration of oxygen in the apparatus was 60 to 66%, for three days it was 52 to 60%, and for 25 days it was 44 to 52%. It is regarded as highly probable that the high oxygen concentration was the cause of the retrolental fibroplasia. A rapid removal from the oxygen-rich to the atmospheric air may also play a role in causation.

AMBERG, Rochester, Minn.

LIPOCHONDRODYSTROPHY (GARGOYLISM, HURLER'S SYNDROME) WITH SPECIFIC CUTANEOUS DEPOSITS. BJARNE ANDERSSON and OLAV TANDBERG, Acta Paediat. **41**:162 (March) 1952.

A peculiar skin lesion in a 6½-year-old boy with gargoylism is described. Biopsy showed vacuolated cells just below the epithelial membrane. These cells had the same microscopic appearance as those appearing in the internal organs of patients with gargoylism who have died. They also reacted in the same manner to various stains. A considerably increased thickness of the dermis with abundant formation of hyalin and collagenous bundles was also observed.

FROM THE AUTHORS' SUMMARY.

FAMILIAL INFERIORITY OF THE DIENCEPHALON AND HEREDITARY BRACHYDACTYLY. D. P. R. KEIZER, Nederl. tijdschr. verlosk. en gynaec. **95**:1565 (May 26) 1951.

This is a description of a family in which brachydactyly was dominantly hereditary, diencephalic disturbances occurring as well.

VAN CREVELD, Amsterdam, Netherlands.

Newborn

CONGENITAL ATRESIA OF THE BILE DUCTS ASSOCIATED WITH ERYTHROBLASTOSIS FETALIS. JOHN T. MCGEEHAN, JAMES BAIRD BUTCHART, and DUDLEY P. WALKER, J. Pediat. **39**:575 (Nov.) 1951.

The authors think that in this case the congenital atresia of the bile ducts is independent of and not related to the erythroblastosis in the same patient. They recommend blood transfusions for the erythroblastosis and watchful waiting until the child's condition is optimal for surgery and until the diagnosis of extrahepatic biliary obstruction is fairly well assured.

MACDONALD, Pittsburgh.

COAGULATION STUDIES IN THE NEWBORN INFANT. B. J. GROSSMAN, R. M. HEYN, and I. H. ROZENFELD, Pediatrics **9**:182 (Feb.) 1952.

Data on the whole-blood-clotting time, platelet count, prothrombin concentration, protamine titration, and gross observation for clot lysis are presented on 21 normal newborn infants within the first six hours after birth and also on the third and fifth days of life. In addition, data on 35 normal newborn infants, studied in groups of 5 through the first seven days of life with the above techniques and the addition of the heparin-sensitivity tests, are presented.

The significance of the data is discussed.

FROM THE AUTHORS' SUMMARY.

OMPHALOCELE. J. E. LEDDY and A. E. BUCKWOLD, Canad. M. A. J. **66**:272 (March) 1952.

Leddy and Buckwold report a case of omphalocele in which repair was delayed till 43 days after birth. After the first stage operation, very large inguinal hernias developed, which the authors feel acted as a safety valve in providing additional room for the abdominal viscera.

MCGUIGAN, Evanston, Ill.

RADIAL NERVE PALSY ASSOCIATED WITH LOCALIZED SUBCUTANEOUS FAT NECROSIS IN THE NEWBORN. REGINALD LIGHTWOOD, Arch. Dis. Childhood **26**:437 (Oct.) 1951.

The presence of wristdrop demands a search for its cause; if it is unilateral the cause will be local. Two cases of this nature in newborn infants are described. The wristdrop was associated with a small patch of sclerema forming over the supracondylar portion of the radial nerve just above the elbow. This showed the topography of the condition and enabled all suspicion of brachial plexus injury to be excluded. The association is rare, and the prognosis apparently excellent.

KELLY, Milwaukee.

THE RADIOLOGICAL "DOUBLE CONTOUR" EFFECT IN THE LONG BONES OF NEWLY BORN INFANTS. N. M. HANCOX, J. D. HAY, W. S. HOLDEN, P. D. MOSS, and A. S. WHITEHEAD, Arch. Dis. Childhood **26**:548 (Dec.) 1951.

An investigation into the occurrence and cause of a double contour effect in roentgenograms of the long bones of infants is described. Theories of causation are discussed, and evidence is submitted in favor of its being due to local exaggeration of the normal growth process.

KELLY, Milwaukee.

UNUSUALLY GREAT CEPHALHEMATOMA IN A NEWLY BORN INFANT. K. ÁCS, Orvosok lapja **4**:1614 (Dec. 12) 1948.

A newly born infant with a body weight of 3,780 gm. showed a head circumference of 34 cm. which increased to 39 cm. in two days. Meanwhile the infant became anemic and sleepy. The roentgenogram showed that the normal skull was surrounded with a 2-cm.-thick, soft tissue. The postmortem examination revealed that under the skin of the head there was a 1.5-cm.-thick hematoma to be found, which covered the whole skull. No traumatic injury could be detected on the skull, and in the intracranial cavity neither any injury nor any bleeding was to be found. The other organs, apart from some little petechiae, were normal. Ács suggests that the unusually

great cephalhematoma was caused by a severe hypoprothrombinemia. To avoid these unexpected great hematomas, Ács recommends the administration of 10 mg. vitamin K orally to every newly born infant immediately after the birth and the repetition of the same dose on the second day of life.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

CLINICAL, HEMATOLOGICAL, AND SEROLOGICAL SYMPTOMS IN NEWBORN SUFFERING FROM HEMOLYTIC DISEASE OF THE NEWBORN DUE TO RH ANTAGONISM. J. M. SOETERS, Maandschr. Kindergeneesk. **18**:160 (No. 3/4) 1950.

The following serological problems are raised: (1) whether the child actually inherits the antigen of the father; (2) whether the maternal antibodies can be detected absorbed on the erythrocytes of the child (Coombs test); (3) whether the placenta contains antigens (van Bolhuis).

It has not infrequently been seen that the mother has antibodies in her blood during pregnancy, the titer of which even increases, and yet a Rh-negative child is born. This should be understood when it is known that the father is a heterozygote. Although at first it seemed as though the course of the antibody titer of the mother during pregnancy enabled us to prophesy the condition of the child, it has now become apparent that low titers may result in seriously diseased children, and high titers, even titers that rise during the last months of pregnancy, may result in less seriously affected children.

In spite of a growing knowledge of this subject, it becomes ever more difficult to formulate clear indications. It is a matter of weighing pros and cons, and once therapy is begun, the physician can but wait to find whether the dreaded nuclear damage will reveal itself, thereby giving a bad prognosis for the child.

FROM THE AUTHOR'S SUMMARY.

Acute Contagious Diseases

LANSING POLIOMYELITIS VIRUS NEUTRALIZING ANTIBODY TITERS OF DIFFERENT TYPES OF HUMAN SERUM. S. O. LEVINSON, A. MILZER, and A. WOLF, Illinois M. J. **100**:238 (Oct.) 1951.

There is considerable variation in the potency of Lansing neutralizing-antibody titers of poliomyelitis convalescent serum, depending upon the type of poliomyelitis suffered by the donor and the time elapsed since the attack.

The most potent serum, with the highest titer of Lansing neutralizing antibodies, is obtained from donors who suffered an attack of poliomyelitis with the spinal type of paralysis. The next in potency is obtained from donors who suffered an attack of poliomyelitis with the bulbar type of paralysis. Persons with nonparalytic poliomyelitis give serum low in titer and should not serve as donors of poliomyelitis convalescent serum.

The optimum period for blood donations is within the five years following the attack. No donor should serve 10 years after his attack. Gamma globulin prepared from normal human plasma shows a relatively high titer and might be of value for the protection of intimately exposed contacts.

The variable results reported from the use of convalescent serum in the therapy of poliomyelitis may be attributed to variations in the titer of virus-neutralizing antibodies of the administered materials.

FROM THE AUTHORS' SUMMARY.

TRANSMISSION OF POLIOMYELITIS VIRUS. ALBERT B. SABIN, J. Pediat. **39**:519 (Nov.) 1951.

Human feces derived from patients and from healthy carriers is the most important source of poliomyelitis in nature. Entry of the virus by way of the mouth is the usual mode of infection. There is no evidence that the disease is transmitted by droplet nuclei. Sabin suggests the following rules for persons during epidemics: (*a*) Wash hands before eating, and keep fingers out of mouth. (*b*) Keep flies away from all food, and thoroughly wash all uncooked food, e. g., vegetables, fruit, etc. (*c*) Children under 16 years of age should avoid crowded public wading and swimming pools. (*d*) Avoid intimate association with members of a family in which poliomyelitis has occurred within the past three weeks.

MACDONALD, Pittsburgh.

BULBAR POLIOMYELITIS: A RESPIRATORY PROBLEM. T. C. GALLOWAY and JOHN ELSEN, Laryngoscope **61**:548 (June) 1951.

In bulbar poliomyelitis, secretional obstruction, anoxia, and carbon dioxide accumulation are more deadly than is the direct action of the virus on the vital centers. It follows that treatment of the former gives the better results. Such treatment, not only by Elsen and Galloway but also by others, produced a distinct (two-thirds) lowering of the mortality rate. The lethal damage is caused both by a lack of oxygen and (much more so) by an accumulation of carbon dioxide, which quickly produces a dangerous lowering of the pH. Treatment, therefore, should be directed not only toward increasing the oxygen but also toward reducing the carbon dioxide concentration.

Secondary effects of secretional obstruction must be looked for. These include congestion, edema, atelectasis, etc., of the airways and lung. Inability to swallow leads to similar trouble. Postural drainage, suction, administration of oxygen, and tracheotomy are included in the therapy of the condition. Maintaining a clear airway is the goal. Food, fluids, and vitamins are administered parenterally meanwhile.

The laryngologist and trained personnel constantly in attendance obviously are necessary.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

LIGHT PARALYTIC FORMS OF EPIDEMIC POLIOMYELITIS: EARLY IDENTIFICATION BY ELECTRICAL EXAMINATION. M. BERNHEIM, C. BERAUD, and P. BRUEL, Pédiatrie **39**:583, 1950.

Eight cases of slightly paralytic poliomyelitis with complete recovery were observed. The authors found that by means of faradic muscular stimulation they could give an early prognostic evaluation regarding the degree of permanent muscular damage.

GLASER, Jerusalem.

THE POLIOENCEPHALITIC FORM OF EPIDEMIC INFANTILE PARALYSIS. P. KNUCHEL, Schweiz. med. Wchnschr. **82**:388 (April 12) 1952.

In a children's hospital, 20 patients with poliomyelitis were observed during the fall of 1951. Of these, 11 had paralysis, and 4 of these had encephalitic symptoms. The author agrees with others that the encephalitic form of poliomyelitis is becoming more frequent.

AMBERG, Rochester, Minn.

PENICILLIN TREATMENT OF SCARLET FEVER. H. JEBENS, Ztschr. u. Kinderh. **68**:303, 1950.

One hundred sixty-one patients with scarlet fever were studied under isolation conditions, 80 treated with penicillin and 81 alternating patients not treated. Twenty-four hours after treatment with penicillin was started 86% had no more streptococci in the throat, after 48 hours 97%, and after three days 100%. Thirty children showed reappearance of streptococci after administration of penicillin was discontinued, and six transmitted the disease upon their discharge. Early discharge from the hospital is beneficial for the patient (prevention of reinfection and complication) but is contraindicated when streptococci have reappeared. Complications occurred in 26% of the treated and 71% of the untreated patients, and it seems that the complications of the first group occurred after reinfection or in patients for whom treatment was started late. The recurrence of streptococci in patients who were removed from exposure is explained by the bacteriostatic and not bactericidal action of penicillin. Patients in whom streptococci reappear at the hospital have more complications and cause a greater number of secondary cases than those whose reinfection occurred at home. This is explained by the great variety of types of streptococci present in the hospital as compared with only the patient's type in his home. For the same reason patients reinfected in the hospital proved particularly infectious upon their discharge. No penicillin-resistant organisms were found, and, after termination of the experiment, when all patients in the hospital were treated with penicillin, no reinfections occurred in the hospital.

Immunity, as tested by the ability of the serum to efface the exanthema, was found to be weaker in early and vigorously treated patients than in untreated or late-treated patients.

Jebens recommends early penicillin treatment of scarlet fever and discharge of the patient while still under the protection of penicillin.

GLASER, Jerusalem.

FEVER THERAPY WITH A COLI VACCINE IN POLIOMYELITIS. F. DÉMANT and G. BÁRDOŠOVÁ, Pediat. listy **5**:193 (No. 4) 1950.

The authors elaborated a method of treating patients with poliomyelitis, taking into consideration the anatomy of the blood supply to the spinal cord and the pathologico-anatomical changes in the muscles and spinal cord in poliomyelitis. This method was used in 43 patients out of a total of 95 who were admitted to the Children's Clinic at Kosice with the diagnosis of poliomyelitis in the years 1945 to 1949. They began to use this method of treatment in 1947. Only severe cases were selected. This treatment led to complete recovery in 20, a great improvement in 16, and little improvement in 7 patients. Treatment was by fever therapy, using the method described by Prof. Lukes. A killed coli vaccine was administered in increasing doses, 8 to 10 injections being given on alternate days, in two to three courses. This treatment is tolerated much better by children than it is by adults. An improved blood supply to the spinal cord and muscles is insured by the fever therapy, the permeability of the cerebrospinal-blood barrier is increased, and the defensive powers of the organism are enhanced by the stimulation of the reticuloendothelial system. Treatment was started as early as the end of the first week if the general state of the patient permitted, whereas other authors like Acquu did not commence therapy earlier than one to two years after the acute stage.

FROM THE AUTHORS' SUMMARY.

Acute Infectious Diseases

SUPERFICIAL FUNGUS INFECTIONS—THE DIRECT MOUNT AND CULTURE IN TINEA PEDIS. DAVID COHEN and MILTON GOLDIN, Illinois M. J. **100**:252 (Oct.) 1951.

In a series of 1,000 cases of possible tinea pedis direct mounts were positive for fungi in 48.8%, and cultures were positive in only 32.4% of these 488 cases. Possibilities to account for the low percentage of positive cultures as compared with the positive direct mounts are discussed.

FROM THE AUTHORS' SUMMARY.

FATAL CANICOLA FEVER WITH AUTOPSY FINDINGS. E. P. LEROY, A. GOODMAN, M. GOLDIN, and S. J. BOLONIK, Pediatrics **9**:20 (Jan.) 1952.

A 6-year-old white boy died in coma five days after his admission to Mount Sinai Hospital, Chicago. He had fever, jaundice, and hepatomegaly with moderate neutrophilic leucocytosis; further laboratory studies were compatible with severe functional impairment of the liver.

Viral hepatitis was diagnosed clinically.

Postmortem examination revealed a subacute hepatitis which, as established by agglutination tests (titer 1:1,028), was due to *Leptospira canicola*. This is the first recorded case of canicola fever in a child and the fourth one to be fatal.

FROM THE AUTHORS' SUMMARY.

RHEUMATIC HEART DISEASE IN NATIVE ALGERIAN CHILDREN: A STATISTICAL STUDY. CH. SARROUY and R. VENEZIA, Pédiatrie **39**:867, 1950.

An increase in rheumatism and rheumatic heart disease in children during the last years has been noted in Algeria and corresponds to reports from other subtropical and tropical countries.

GLASER, Jerusalem.

STUDY OF ALKAPTONURIA. E. MARTIN, G. MILHAUD, B. COURVOISIER, and A. LAPINÉ, Schweiz. med. Wchnschr. **80**:981 (Sept. 9) 1950.

Two brothers, ages 8 and 6 years, were studied. Their 24-hour excretion of homogentisic acid varied from 4 to 8 gm. The urinary amino acids of the urine, determined chromatographic-

ally, were the same as in a control. If an alkaline solvent (collidine/water) is used, homogentisic acid can be demonstrated in the paper chromatogram, since on drying the paper a brown spot appears spontaneously. As little as 2.5 γ of the acid can be demonstrated. The R_f (distance of the spot from the starting line divided by the distance the solvent traveled on the paper) is 0.8. The administration of dl-phenylaminopropionic acid or of tyrosine increased the urinary homogentisic acid. The administration of large doses of ascorbic acid (1.5 to 2 gm.) diminished the elimination of homogentisic acid. In these boys the basal metabolism was increased. One was given 125 mg. of 4-methylthiouracil daily for 10 days with notable diminution of homogentisic acid excretion. These studies could not be pursued further, so the authors advise that reserve be exercised in the evaluation of the results. Among the 31 members of the family examined, no other case of alkaptomuria is known.

AMBERG, Rochester, Minn.

DISEASES DUE TO SALMONELLA PANAMA IN INFANTS AND CHILDREN. H. HENCKEL and G. RENZ, Deutsche med. Wchnschr. **77**:326 (March 14) 1952.

Fourteen cases of infants infected with Salmonella panama and one with Salmonella cahu are discussed. It is noted that the clinical picture does not present features which might facilitate the diagnosis. With various antibiotics, it was possible to render the stools free from the Salmonella, with exception of one case. The administration may have to be rather prolonged. A negative third stool culture was obtained after a period of two weeks to 74 days.

AMBERG, Rochester, Minn.

A NEW NEUROLOGIC COMPLICATION OF INFECTIOUS MONONUCLEOSIS. H. KALK and J. ULBRICHT, Deutsche med. Wchnschr. **77**:397 (March 28) 1952.

Infectious mononucleosis in a 16-year-old girl was complicated by meningitis. It is claimed to be the first such case reported in Germany. Rapid improvement of this complication followed treatment with penicillin combined with streptomycin.

AMBERG, Rochester, Minn.

LISTERIOSIS IN MAN. H. SEELIGER, F. JUNG, G. LINZENMEIER, and H. ODENTHAL, Deutsche med. Wchnschr. **77**:583 (May 2) 1952.

A case of infection with Listeria monocytogenes in an adult is reported. Attention is called to the possibility that this organism may be among the etiologic factors of infectious mononucleosis.

AMBERG, Rochester, Minn.

ADDENDUM: ETIOLOGY OF GRANULOMATOSIS INFANTISEPTICA AND PSEUDO-TUBERCULOUS DISEASES. HEINZ SEELIGER, Deutsche med. Wchnschr. **77**:587 (May 2) 1952.

Within a year, in a certain district a very rare infectious disease, granulomatosis infantiseptica, was reported among newborns and infants (Reiss, Potel, and Krebs). It was possible to isolate Listeria monocytogenes. It is assumed that cases described as pseudotuberculosis might be cases of Listeriosis.

AMBERG, Rochester, Minn.

SIGNIFICANCE OF SEROLOGICAL REACTIONS IN THE DIAGNOSIS OF RHEUMATIC DISEASES. S. A. DEN OUDSTEN and P. E. VAN LOGHEM-LANGEREIS, Nederl. tijdschr. geneesk. **95**:289 (Jan. 27) 1951.

This is a description of four cases of rheumatoid arthritis with an atypical course, in which serological reactions supported the diagnosis.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

CLINICAL TOXOPLASMOSIS: CLINICAL, HISTOPATHOLOGIC, AND PARASITOLOGIC OBSERVATIONS DURING LIFE AND AT POST MORTEM. SVEN GARD, J. HENNING MAGNUSSON, F. WAHLGREN, and GUNNAR GILLE, Pediatrics **4**:432 (Oct.) 1949.

An account is given of congenital toxoplasmosis in a child who died at the age of 43 days. The patient, who from birth was somnolent, showed the following main symptoms: bilateral

microphthalmia and chronic bilateral uveitis with secondary cataract; marked hydrocephalus internus, mainly symmetric, cerebral calcifications, pronounced typical changes in the cerebrospinal fluid, hypoprothrombinemia, and eosinophilia; enlargement of the liver and spleen; marked lability of the body temperature with wide variations.

The postmortem findings, both macroscopic and microscopic, were typical in every respect, with pronounced necrotic encephalitis in the cerebrum and characteristic foci of granulomata in the brain stem and the spinal cord. Toxoplasma pseudocysts were demonstrated in the affected parts of the brain. Typical Toxoplasma were isolated from the spinal fluid on three occasions, from material obtained by liver biopsy, and from pieces of brain and spleen removed at autopsy.

Serum from the patient as well as from the mother gave a positive neutralization test in rabbits. The in vitro dye test, according to Sabin and Feldman, yielded a positive result with a high titer value.

The strain of Toxoplasma isolated ("G. L.") seems to be serologically identical with the American strains "RH" and "LM." [RH was used by Feldman, A. M. A. Am. J. Dis. Child. **83**:74 (Jan.) 1952.]

From the Authors' Summary.

Streptomycin and Primary Tuberculosis in Infancy. G. Mouriquand, N. Boulez, D. Dechavanne, F. Favard, and F. Ruesch, Pédiatrie **39**:137 (No. 1) 1950.

The authors state that, although primary tuberculosis discovered by routine examination may not warrant treatment, the treatment with streptomycin is definitely indicated if the general health of the infant is affected, since the incidence of tuberculous meningitis is high and its treatment unsatisfactory.

Glaser, Jerusalem.

Toxoplasmosis in Human Neurology. F. Bamatter and H. Habegger, Schweiz. med. Wchnschr. **82**:372 (April 12) 1952.

The authors discuss toxoplasmosis. The frequency of neurological and ophthalmic symptoms is tabulated from the records of 74 cases of congenital toxoplasmosis in patients dying during the first year of life, the diagnosis being confirmed by histopathologic examination.

Amberg, Rochester, Minn.

From the Nosological to the Functional Viewpoint of Nephropathies. G. Fanconi, Schweiz. med. Wchnschr. **82**:404 (April 12) 1952.

It is hardly possible to do justice to the paper in an abstract; it is recommended that the original be consulted.

Amberg, Rochester, Minn.

Should BCG Vaccination Be Made Obligatory? A. Wallgren, Schweiz. med. Wchnschr. **82**:422 (April 12) 1952.

In Sweden, it is unnecessary to make BCG vaccination obligatory, since the population responded voluntarily to propaganda and publication of the results. This should be continued. Neither is it recommended that the vaccination should be made obligatory in other civilized countries.

Amberg, Rochester, Minn.

Precocious Sexual Development. B. Carletti, Minerva pediat. **4**:9 (Jan. 15) 1952.

Enlargement of the breasts was noted to be developing in a girl at the age of 22 months; a few weeks later she began to menstruate at regular intervals. Extensive clinical, psychological, and anthropometric studies were made when she was 25 months old and again at 44 months. She was very large physically; her bone age was set by x-ray studies as 4½ and 11 years at the times she was studied. The only striking abnormality on physical examination was a peculiar spasm of the ocular muscles; the cause for this could not be accurately placed but may have been in the diencephalon or in the mesencephalon. The child's condition was diagnosed as precocious sexual maturity, brought on by an undetermined cerebral process.

Higgins, Boston.

EXPERIENCE IN TREATMENT OF TUBERCULOUS MENINGITIS IN CHILDREN. L. AURICCHIO, Pediatria **58**:289 (May) 1950.

At the Pediatric Clinic in Naples 104 children with tuberculous meningitis have been treated since 1947. Of these, six are cured and four improved; in nine the disease has remained stationary, and the others have died. Each received streptomycin therapy. The most satisfactory results were obtained when the daily doses of streptomycin were 100 to 200 mg. intraspinally and 100 mg. per kilogram of body weight intramuscularly. Of 29 patients to whom this dose was given, 3 are well, 4 are improved, 8 have stationary disease, and 14 have died. The other 74 patients received smaller doses of streptomycin. Sulfonamides were found to be of value as supplementary medication, but paraaminosalicylic acid was of no benefit. Vitamins A and D, together with proper dietary controls, were beneficial.

The author does not believe that streptomycin is the cause of the spinal blockage and dilation of the ventricles seen in so many cases of tuberculous meningitis.

HIGGINS, Boston.

TUBERCULOUS BACILLEMIA. JOSÉ ANGEL DE ARGUMOSA Y VALDEZ, Acta pediat. espaň. **92**:935 (Aug.) 1950.

The author believes that with the introduction of streptomycin in the treatment of tuberculosis, it is necessary to clarify some of the thinking regarding tuberculosis in children. Diagnosis is difficult in the period before the infection becomes localized.

A bacillemia is a clinical manifestation due to the tubercle bacillus in the blood, but with no demonstrable metastatic or local manifestations. The author mentions several cases in which the disease was diagnosed as typhoid, whooping cough, etc.; after a period of prolonged fever with no other symptoms the disease later developed into full-blown tuberculous meningitis or miliary tuberculosis. In such cases with fever and no other symptoms or signs, tuberculosis should always be suspected, especially if the patient has relatives with tuberculosis.

The table of comparison elaborated by Hegler to differentiate between miliary tuberculosis and typhoid is given with the admonition that only certain parts can be used because there naturally are no localized areas at the time when the disease may be accurately referred to as a bacillemia. This disease has been called by various names and has usually been found only on autopsy. The older pathologists of Germany called it typhoid-tuberculosis, tuberculous bacillemia, acute tuberculous sepsis. However, the author insists that there must be a focus to provide the circulating organisms noted in the blood because the bacilli are not capable of reproducing in the blood stream.

ALLEN, Santa Fe, N. M.

INFECTION WITH MEASLES VIRUS AS THERAPY OF A NEPHROTIC SYNDROME. KHO LIEN KENG and F. KUIPERS, Nederl. tijdschr. geneesk **95**:1806 (June 23) 1951.

Two children with chronic glomerulonephritis and the nephrotic syndrome showed improvement after inoculation with the virus of measles. The virus was obtained by intramuscular injection of citrated blood or plasma from patients suffering from measles.

The first patient showed a complete disappearance of the nephrotic syndrome, after treatment with corticotropin (ACTH) had failed. In the second patient, the syndrome returned after a short improvement.

VAN CREVELD, Amsterdam, Netherlands.

SUBCUTANEOUS PYELOGRAPHY IN CHILDREN. N. J. BAKKER, Nederl. tijdschr. geneesk. **95**:3167 (Oct. 27) 1951.

The author describes the procedure of subcutaneous pyelography and gives two case histories. Especially for infants and young children, in whom intravenous injection is impossible or very difficult, this method is suitable.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Blood, Heart and Blood Vessels and Spleen

PRE- AND POSTOPERATIVE CAPILLAROSCOPY IN CONGENITAL HEART DEFECTS. E. ROSSI, M. GROB, and J. GUTEWA, Helvet. paediat. acta **5**:279 (June) 1950.

Capillary changes in the nail fold were observed under the capillary microscope in 51 children suffering from congenital heart disease. When the observations were correlated with other blood findings, it was noted that the abnormal changes in the capillaries ran parallel to the degree of cyanosis and related symptoms. The most pronounced changes were observed in deeply cyanotic cases belonging to the tetralogy of Fallot. The capillary loops are greatly increased in this condition, and they run a tortuous course, especially in the venous limb. Their lumen is enlarged from 0.01 to 0.027 mm. (normal 0.008) in diameter in the afferent limb, and the over-all length is increased. In the efferent limb the lumen varies from 0.02 to 0.055 mm. (normal 0.014) in diameter. On the whole, the efferent branches are more affected than the afferent ones as far as lengthening and twisting are concerned.

Capillary changes are less marked in conditions that show a more variable state of cyanosis, for example the Eisenmenger complex and truncus arteriosus communis (verus and pseudo); although on the whole they resemble those observed in the tetralogy of Fallot. In one case of truncus arteriosus communis, where cyanosis was the outstanding symptom, the capillary changes were identical with those observed in a severely cyanotic case of tetralogy of Fallot. Patent foramen ovale or a defective intraventricular septum were also examined for the sake of comparison, but the capillary network is almost normal in these latter conditions.

In cases of stenosis of the isthmus of the aorta, capillary changes are produced that resemble those found associated with hypertension. The capillary loops are elongated and their afferent limbs are narrow and spastic. In a number of cases the capillary changes were observed before and after operative intervention. A distinct improvement in the pathological capillary network can be observed as early as three weeks after the operation. In one case of stenosis of the isthmus of the aorta, resection was followed by a complete restoration of the capillary pattern. Capillaroscopy is an objective means of assessing relatively early the benefit derived from operation in these cases.

FROM THE AUTHORS' SUMMARY.

CASE OF LYMPHATIC LEUKEMIA IN BICHORIAL TWINS. ALESSANDRO BIEBER, Riv. clin. pediat. **48**:161 (March) 1951.

The author describes a very rare clinical case of bichorial, bisexual twins both affected a brief interval apart by a very serious and swiftly lethal form of lymphatic leukemia; this case is especially interesting for the similar clinical findings in spite of the fact that the twins were bichorial.

The interesting biological aspect of this observation is emphasized. It would confirm the importance of parental heredity, a common hereditary predisposition regulated by one or more genes, transmitted by both parents and present in the genetic heritage of both brothers, on which the acquired constitution has acted—though it is not dependent on the well-known laws of heredity but on the identical influence of surroundings during ontogenesis.

Great importance is attached to this second factor in the heredity of leukemias, and particularly in lymphatic leukemia. Added to this predisposition, factors of an hypothetical infective nature might have caused in the two twins the illness observed.

FROM THE AUTHOR'S SUMMARY.

Diseases of Lungs, Pleura, and Mediastinum

ADVANCES IN THERAPY OF PLURAL EMPYEMA IN BABIES, WITH PARTICULAR REGARD TO THE LOCAL ACTION OF SULFONAMIDES AND PENICILLIN. G. CADEDDU and L. SCALAS, Ann. ital. pediat. **2**:91 (April) 1949.

The authors, on the basis of their examination of 80 children affected with purulent pleurisy who were given medical treatment, confirm that bloodless treatment of the purulent pleurisies is particularly efficacious for children, especially during the first two years of life. It is effected by a daily intrapleuric injection of 30 to 50,000 units of penicillin after a pleural washing with a

5 per cent sulfonamide solution repeated every two or three days and with the "S. W. Therapy." With this method, advised by the authors for all cases of purulent pleurisy, they always obtained recovery without any notable disadvantages.

FROM THE AUTHORS' SUMMARY.

PENICILLIN AND STREPTOMYCIN IN PULMONARY BRONCHOMEDIASTINAL LYMPHOGLANDULAR AFFECTIONS AND IN OTHER EXTRARESPIRATORY INFECTIONS IN CHILDHOOD. C. TACCONE, Riv. clin. pediat. **47**:129 (Feb.) 1949.

The author gives the anatomic and biologic elements on which he was induced to the systematic use of antibiotics (penicillin and streptomycin), injected in the pleural cavity for the treatment of the diseases of the lungs and tracheobronchial lymph nodes. He considers 70 cases, including 4 of croupous pneumonia, 36 of bronchopneumonia and 30 of various tuberculous conditions of the chest: involvement of the hilar and tracheobronchial lymph nodes, tuberculous postprimary infiltrations, tuberculous bronchopneumonia, disseminated tuberculosis with and without meningitis. He reports the results obtained by treatment. In the acute conditions a single inoculation is often sufficient; for tuberculosis the inoculation must be repeated several times. The doses for penicillin are 50,000 units, for streptomycin, 0.20 to 0.40 gm. each dose. The author points out the poor results in poliomyelitis and the good, often excellent, results in cases of toxicosis of newborn children and typhoid.

FROM THE AUTHOR'S SUMMARY.

INTERSTITIAL PLASMA CELL PNEUMONIA IN INFANTS. HARALD GORMSEN, Acta pædiat. **39**:291 (No. 4-5) 1950.

A report is given of two cases, verified by autopsy, of interstitial plasma cell pneumonia in premature infants, aged 12 and 14 weeks respectively, who died after two days and two weeks of illness. In this connection a survey is given of the occurrence, pathology, clinical aspects, and treatment of interstitial plasma cell pneumonia.

It is a striking fact that 85% of the published cases of this disease, which was first recognized about 15 years ago, have occurred in premature infants, especially in the second or third months of life, and that hitherto the disease appears to have been observed only in Germany, Austria, Switzerland, and the Scandinavian countries.

The theories advanced concerning the unknown etiology and pathogenesis of the disease are reviewed. It seems most likely to involve an infection (with a virus?) which, on account of particular conditions (hypoproteinemia, hypo-gamma-globulinemia, and low resistance?) gives rise in the organism of premature and weak infants to the very characteristic changes found in the lungs.

FROM THE AUTHOR'S SUMMARY.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

TREATMENT OF TYPHOID FEVER WITH CHLOROMYCETIN: REPORT OF FOUR CASES. GUSTAF W. ERICKSON, New England J. Med. **242**:177 (Feb. 2) 1950.

Treatment with chloramphenicol (chloromycetin®) of patients in the acute, carrier, and relapse stages of typhoid is presented. The drug was given in a dosage of 50 mg. per kilogram of body weight at once followed by 50 mg. per kilogram of body weight daily for either an 18 to 20 gm. total dose or until the temperature had been normal for seven days.

Clinical improvement and normal blood and stool cultures were noted within 72 hours of treatment with chloramphenicol. No toxic reactions or untoward side-effects were noted during the course of therapy in three patients.

WHEELOCK, Denver.

CONGENITAL FAMILIAL NONHEMOLYTIC JAUNDICE. EUGENE STRANSKY, Ann. pædiat. **175**:301 (Oct.) 1950.

A relatively new syndrome, first described by Rotor, Manahan, and Florentin, is investigated. The syndrome is marked by jaundice caused by an accumulation in the body of hepatic crystalloid bilirubin in the absence of an occlusion of the biliary passages and without any further liver damage. The syndrome is congenital and familial. Although the first signs can be

observed in early infancy, it appears that the jaundice becomes latent during infancy, for some unknown reason, but manifests itself later again and persists throughout life. The etiology is completely unclear. The disturbance is confined to the biliary metabolism.

FROM THE AUTHOR'S SUMMARY.

THIRTY-SIX YEARS OF PAPAVERINE TREATMENT IN PYLOROSPASM IN THE NEWBORN AND YOUNG INFANT. E. MAYERHOFER, Ann. pædiat. **176**:73 (Feb.) 1951.

Mayerhofer gives a description of the systematic papaverine therapy which he has been using for 36 years in the treatment of true hypertrophic pyloric stenosis. The muscular hypertrophy is preceded by a simple functional spasm, which is one of the symptoms belonging to the allergic syndrome described by the author. It is at this moment that treatment should start, thus preventing the development of muscular hypertrophy. Apart from this effect, the treatment of this frequent allergic spasm with papaverine often helps toward successful prevention of serious difficulties in breast feeding, and so of early nutritional upsets.

Recommended doses: 0.01 gm. of papaverine combined with 0.05 gm. of aminopyrine (amidopyrine) three or four times a day, before meals. If this medication is unfeasible because of the patient's vomiting, the drugs can be given as suppositories or medicated enemas, or the hydrochloride of papaverine can be injected. The author stresses the importance of the neuropathic factor in pyloric stenosis.

FROM THE AUTHOR'S SUMMARY.

CLINICAL COURSE AND EFFECTS OF TREATMENT IN DYSPEPSIA AND ENTEROCOLITIS OF INFANTS, IN RELATION TO THE FECAL FLORA. G. R. BURGIO, B. CIMINO, and L. BAVASTRELLI, Lattante **21**:489 (Aug.) 1950.

The only important coliform organisms in the stools of infants with dyspepsia are Escherichia coli; but in the stools of infants with enterocolitis or with dysentery, Shigella dysenteriae, Proteus, or lactose-fermenting E. coli may be found in considerable numbers. Streptomycin therapy is quite efficacious in cases in which the dysentery bacilli are present in the stools. Proteus and lactose-fermenting E. coli are more resistant to streptomycin; this appears to explain why sulfathiazole and sulfadiazine are more efficacious in the treatment of patients in whose fecal flora these organisms are present.

HIGGINS, Boston.

A CASE OF RACHITIS HEPATICA. (HEPATIC RICKETS). ILSE TEUBER, Arch. Kinderh. **134**:211, 1948.

Histological examination revealed indubitable rickets in the bones of a 5½-month-old infant who died of congenital atresia of the extrahepatic ducts and cholostatic cirrhosis of the liver. According to Gerstenberger, this incidence of rickets is explained by inhibition of the absorption of vitamin D because of the lack of bile acids.

ARON, Chicago.

PATHOGENESIS AND THERAPY OF CELIAC DISEASE. J. DIECKHOFF, Arch. Kinderh. **138**:161 (March) 1950.

Six patients were treated in the first period with an adrenal cortex extract desoxycorticosterone acetate (percorten®) only; in the following period the same extract was given in combination with 5 mg. riboflavin (vitamin B_2) and 100 mg. nicotinamide, injected twice daily for 14 to 21 days. After this combined hormone-plus-vitamin-B therapy, a definite improvement was observed. The stools approached normal condition, higher values for the absorption of fat, carbohydrate, calcium, and phosphorus were found.

ARON, Chicago.

CLINICAL CONTRIBUTION CONCERNING PATHOLOGY OF THE LIVER DURING INFANCY. F. A. KUSKE, Arch. Kinderh. **142**:132 (No. 3) 1951.

A detailed description of two cases is presented, the first one showing acute cellular hepatic degeneration, the second, focal necrosis. Both cases were studied histologically. The author

discusses various etiological possibilities, such as preceding intestinal disorders, infections, and the use of barbiturates. He also emphasized a possible relationship between pylorospasm and succeeding hepatic damage. A disorder of the vegetative regulation which regulates the pyloric activity may also involve the liver functions.

GOTTSTEIN, Chicago.

FOREIGN BODIES IN ESOPHAGUS AND LOWER AIR PASSAGES. ERICH KNAPP, Deutsche med. Wchnschr. **76**:589 (April 27) 1951.

It is emphasized that on suspicion of a foreign body in the esophagus or the air passages a roentgenologic examination should be made. Even if this should be unrevealing, examination by esophagoscopy or tracheobronchoscopy is necessary. Particularly in children tracheobronchoscopy through a tracheotomy opening is preferable, since it allows better manipulation. Very small foreign bodies may be aspirated by means of a tube smaller than a bronchoscopy tube.

AMBERG, Rochester, Minn.

SODIUM AND POTASSIUM CONCENTRATION OF ERYTHROCYTES AND BROMSULFALEIN LIVER FUNCTION TEST IN SEVERE INFANTILE GASTROENTERITIS. JYRKI KAUHTIO and NIILO HALLMAN, Acta pædiat. **39**:328 (No. 4-5) 1950.

A study of the potassium and sodium concentrations in the erythrocytes in 28 infants suffering from severe gastroenteritis is presented. Simultaneously determinations of sulfobromophthalein sodium retention were made and the results compared.

In the majority of cases during the acute stage of the disease the potassium of the erythrocytes decreased and the sodium increased. These changes were controlled while recovery was in progress.

A higher sulfobromophthalein sodium retention than normal was also demonstrated during the disease in the majority of cases. Practically always a clear correlation could be established between these phenomena.

FROM THE AUTHORS' SUMMARY.

CYSTIC FIBROSIS OF THE PANCREAS WITH INTERSTITIAL PLASMOCELLULAR PNEUMONIA. I. VAN DER HAL, Maandschr. kindergeneesk. **18**:381 (No. 10) 1950.

A 6-week-old infant presented the clinical and roentgenographic picture of interstitial plasmocellular pneumonia. An apparently complete recovery was followed by a fatal relapse. Autopsy revealed a congenital pancreatic fibrosis.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL PYLORIC STENOSIS. YUNG-EN KAO, HUNG-YUAN LIN, and YUNG-LOU HWANG, Chinese M. J. **67**:257 (May) 1949.

In Nanking, China, congenital pyloric stenosis was seen once among 25,742 pediatric outpatients.

MACDONALD, Pittsburgh.

News and Comment

ANNOUNCEMENTS

Jacobi Fund.—The Jacobi Fund of the Section on Pediatrics of the A. M. A. received $1,696 from 282 contributors, according to the report made at the June meeting in Chicago by Hugh L. Dwyer, M.D., Custodian. Net income from investments was $188.76. Expense and distribution to essayists was $731.80. Trust value May 30, 1952, was $6,890.04.

Revised Labeling of Chloramphenicol (Chloromycetin®).—The Food and Drug Administration of the Federal Security Agency announced today its decision to permit the continued distribution of the antibiotic drug chloramphenicol under revised labeling that will caution physicians explicitly against its indiscriminate use.

Caution

Certain blood dyscrasias (aplastic anemia, thrombocytopenic purpura, granulocytopenia and pancytopenia) have been associated with the administration of chloramphenicol. It is essential that adequate blood studies be made when prolonged or intermittent administration of this drug is required. Chloramphenicol should not be used indiscriminately or for minor infections.

Blood dyscrasias may be associated with intermittent or prolonged use. It is essential that adequate blood studies be made.

Special Course on "The Premature Infant."—The Premature Infant Center of Charity Hospital of Louisiana at New Orleans will give a special course on "The Premature Infant" Nov. 5 through 19, 1952. This is open to all physicians, and there are no tuition fees.

CORRECTION

In the August, 1952, issue of the ARCHIVES, page 238, the third sentence of the abstract of an article by Scarzella should read, "This treatment results in quick and often dramatic improvement, as shown by general cenesthesia. . . ."

Directory of Pediatric Societies *

INTERNATIONAL

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 16, rue du Mont-Blanc, Geneva, Switzerland.
Place: Bombay, India. Time: Dec. 5-12, 1952.

IV° Congreso Pan-Americano de Pediatria

President: Dr. Leonel Gonzaga.
General Secretary: Dr. Adamastor Barbosa.
Secretariat: Rua Dias da Rocha 25, ap. 602, Copacabana, Rio de Janeiro.
Place. Rio de Janeiro. Time: 1954.

IV° Congreso Sudamericano de Pediatria, Confederacion Sudamericano de Sociedades de Pediatria

President: Prof. Carlos Prado.
Vice President: Dr. Marcelo Garcia.
General Secretary: Dr. Alvaro Aguiar.
Place: Avenida Mem de Sá 197, Rio de Janeiro. Time: 1954.

FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

Chairman: Dr. Bernard Laski, Toronto.
Secretary: Dr. Crawford Anglin, Toronto.
Place: Academy of Medicine.

Australian Paediatric Association

President: Dr. Robert Southby.
Secretary: Dr. J. Colebatch, 12 Collins St., Melbourne.
Place: Canberra. Time: Yearly in April.

Sociedade Brasiliera de Pediatria

For officers, see IV° Congreso Sudamericano de Pediatria, above.

British Paediatric Association

President: Prof. J. Smellie.
Secretary: Prof. Alan Moncrieff, Institute of Child Health, The Hospital for Sick Children, Great Ormond St., W. C. 1, London.
Place: Windermere. Time: Between Easter and Whitsunday.

Canadian Paediatric Society

President: Dr. D. B. Leitch, 210 McLeod Bldg., Edmonton, Al.
Secretary: Dr. R. L. Denton, 1615 Cedar Ave., Montreal 25.

Danish Pediatric Society

President: Dr. A. Rothe-Meyer, Children's Hospital Fûglebakken, Copenhagen F.
Secretary: Dr. E. Winge Flensborg, Children's Hospital Mantinsvej, Copenhagen V.
Place: Different hospitals. Time: First Wednesday of every month.

*Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Departmento de Pediatria da Associação Paulista de Medicina

President: Dr. Oswaldo Riedel de Souza e Silva.
Secretaries: Dr. Ovidio Collesi.
Dr. Helda Elina Vieira de Barros.
Place: Avenida Brigadeiro Luiz Antonio, 278, São Paulo, Brasil.

Deutsche Gesellschaft für Kinderheilkunde

President: Prof. Dr. Adam, Universitats Kinderklinik, Erlangen.
Secretary: Prof. Dr. Jochims, Städtische Kinderklinik, Lübeck.
Place: Bayreuth. **Time:** Sept. 1-4, 1952.

Hellenic Society of Pediatrics

President: Dr. Spiros Charocopos, Alexandras Ave. 1, Athens.
Secretary: Dr. Nikas Zervos.
Place: Amphitheater, Medical School of the University of Athens. **Time:** Once a month.

Nederlandse Vereniging voor Kindergeneeskunde

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. **Time:** Three times a year.

Norsk Pediatrisk Selskap

President: Dr. Arne Njå, Sporveisgt. 29, Oslo.
Secretary: Dr. Helge Granrud, Abbedikollen 38, Bestun, Oslo.
Place: Barneklinikken, Rikshospitalet, Oslo. **Time:** Friday, six times a year.

Pediatric Society of New Zealand

President: Dr. Edward J. Cronin, Power Board Bldg., Queen St., Auckland.
Secretary: Dr. J. D. Matthews, 104 Symonds St., Auckland.
Place: Auckland. **Time:** Sept. 9, 1952.

Philippine Pediatric Society

President: Dr. Renato Ma. Guerrero.
Secretary: Dr. Felix A. Estrada.
Place: Santo Tomas University Hospital and other pediatric centers. **Time:** Every two months.

Royal Society of Medicine, Section of Paediatrics

President: Dr. D. W. Winnicott.
Secretary: Dr. J. J. Kempton; Dr. A. P. Norman.
Place: 1 Wimpole St., London W.1. **Time:** Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft für Pädiatrie

President: P. D. Dr. F. Bamatter, St.-Léger 8, Genève.
Secretary: Dr. M. Nicod, Place Bel-Air 2, Lausanne.

Sociedad Argentinade Pediatrie

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

Sociedad Boliviano de Pediatria

President: Dr. Carlos Daza Meruvia.
Secretary: Dr. Cecilio Abela Deheza.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedad Chihuahuense de Pediatría

President: Dr. Alfonso Ruiz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., México.

Sociedad Chilena de Pediatria

President: Prof. Dr. Raúl Gontes A.
Secretary General: Dr. Edmundo Cardemil M.

Sociedad Cubana De Pediatria

President: Prof. Agustin Castellanos y Gonzales.
Secretary: Dr. Carlos Hernandez Miyares, Apartado 2430, Habana.
Place: Catedra de Clinica Infantil Hospital Nuestra Senora de las Mercedes and Hospital Municipal de Infancia, Habana. Time: 9 p.m., last Wednesday of every month.

Sociedad de Pediatría de Concepción (Chile)

President: Dr. Jacinto Rojas.
Secretary: Dr. Guillermo Repetto D.
Place: Hospital Clinico Reginal Concepción. Time: 7:30 p.m., second Tuesday of every month, April to December, inclusive.

Sociedad de Pediatria del Litord

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary General: Dr. Elsa Galimany.

Sociedade Portugesa de Pediatria

President: Prof. Castro Freire.
Secretary: Dr. Cordeiro Ferreira.
Place: Clinica pediatrica do Hospital D. Estefania, Lisbon. Time: Monthly.

Sociedad Uruguaya de Pediatria

President: Dr. Euclides Peluffo.
Secretary: Dr. Ruben Gorlero Bacigalupi.
Place: Av. Agraciada 1464, piso 13, Montevideo.

Sociedad Venezolana de Puericultura y Pediatría

President: Dr. Guillermo Rangel.
Secretary: Dr. Guillermo Tovar E., P.O. Box 5, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

La Société de Pédiatrie de Montréal

President: Dr. Henri Charbonneau, 3095 Sherbrooke, Montréal.
Secretary: Dr. Edmond Baril, 301 Carré St-Louis, Apt. 1, Montréal.
Time: Second Thursday of each month.

Société de Pédiatrie de Paris

President: Prof. Jean Cathala, 45 rue Scheffer, Paris XVI.

Secretary: Prof. Maurice Lamy, 94 rue de Varenne, Paris VII.

Place: Hôpital des Enfants Malades, 149 rue de Sèvres, Paris XV. Time: 4 p.m., third Tuesday of each month.

Société de Pédiatrie de Québec

President: Dr. Roland Thibaudeau, 203 des Erables, Québec.

Secretary: Dr. Euclide Dechêne, 312 du Roi, Québec.

Place: Quebec. Time: May and November.

Swedish Association of Pediatrics

President: Prof. Sture Siwe, Lund.

Secretary: Dr. Karl-Axel Melin, Färjestadsvägen 16, Bromma.

Swedish Medical Society, Section for Pediatrics and School Hygiene

President: Docent Urban Hjarne, Stockholm.

Secretary: Dr. M. d'Avignon, Pediatric Clinic, Karolinska Sjukhuset, Stockholm 60.

Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm, and Pediatric Clinic, Upsala. Time: Second Friday of each month, except summer.

UNITED STATES

National

American Medical Association, Section on Pediatrics

Chairman: Dr. Walter B. Stewart, 8 N. Tallahassee Ave., Atlantic City, N. J.

Secretary: Dr. Wyman C. C. Cole, 3001 W. Grand Blvd., Detroit.

American Academy of Pediatrics

President: Dr. Warren W. Quillian, 140 Alhambra Circle, Coral Gables, Miami 34, Fla.

Secretary: Dr. E. H. Christopherson, 636 Church St., Evanston, Ill:

Place: Palmer House, Chicago. Time: Oct. 20-23, 1952.

Society for Pediatric Research

President: Dr. Horace Hodes.

Secretary: Dr. Sydney S. Gellis.

The American Pediatric Society

President: Dr. Hugh McCulloch, La Rabida Jackson Park Sanitarium, Chicago 49.

Secretary: Dr. Aims C. McGuinness, 237 Medical Laboratories, University of Pennsylvania, Philadelphia 4.

Sectional

Intermountain Pediatric Society

President: Dr. John T. Mason.

Secretary: Dr. Stanley R. Child.

Place: Ambassador Athletic Club, Salt Lake City. Time: 7 p.m.

New England Pediatric Society

President: Dr. Albert W. Fellows.

Secretary: Dr. Harry Shwachman, 300 Longwood Ave., Boston.

Place: Boston, except Spring meeting. Time: Wednesdays, four times a year.

North Pacific Pediatric Society

President: Dr. Carl Ashley, 2455 N. W. Marshall St., Portland, Ore.

Secretary-Treasurer: Dr. S. Gorham Babson, 1107 S. W. 13th St., Portland, Ore.

Place: Sun Valley, Idaho (1952), Seattle (1953). Time: September, 1952, and March, 1953.

Northwestern Pediatric Society

President: Dr. F. G. Hedenstrom, 420 Lowry Medical Arts Bldg., St. Paul.

Secretary: Dr. Charles L. Steinberg, 1118 Lowry Medical Arts Bldg., St. Paul.

Place: Minneapolis; St. Paul; Duluth, Minn., and Rochester, Minn. Time: January, April, July, and October.

Rocky Mountain Pediatric Society

President: Dr. John Lichty, Pediatric Department, Colorado General Hospital, 4200 E. 9th Ave., Denver.

Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.

Place: Announced by mail. Time: Monthly dinner meetings, October to June.

Southwestern Pediatric Society

President: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.

Secretary: Dr. Carl A. Erickson, 960 E. Green St., Pasadena, Calif.

Place: Jonathan Club of Los Angeles. Time: 6:30 p.m., second Wednesday in January, March, May, September, and November.

State

Alabama Pediatric Society

President: Dr. David B. Monsky, 748 Adams St., Montgomery 5.

Secretary: Dr. Alice H. Pye, 305 Church St., Montgomery.

Place: Montgomery.

Arizona Pediatric Society

President: Dr. Henry E. Running.

Secretary: Dr. William F. Schaffman.

Time: On Call.

California Medical Association, Section on Pediatrics

Chairman: Dr. Joseph W. St. Geme, 511 S. Bonnie Brae, Los Angeles 5.

Secretary: Dr. Alvin H. Jacobs, 2201 Webster St., San Francisco 15.

Assistant Secretary: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills.

Florida State Pediatric Society

President: Dr. E. V. Anderson, The Medical Center, 24 W. Chase St., Pensacola.

Secretary: Dr. J. K. David Jr., 1545 San Marco Blvd., Jacksonville 7.

Place: West Palm Beach. Time: Nov. 8 and 9, 1952.

Georgia Pediatric Society

President: Dr. John A. Simpson, Athens.

Secretary: Dr. J. Harry Lange, 490 Peachtree St., Atlanta.

Place: Savannah. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Joseph Hetzel, 51 Central Ave., Waterbury.

Secretary: Dr. James H. Root Jr., 103 N. Main St., Waterbury.

Time: With the Connecticut State Medical Society in the spring, with the Connecticut State Clinical Congress in the fall; winter meeting usually in December.

Illinois State Medical Society, Section on Pediatrics

Chairman: Howard R. Miller, 418 Jefferson Bldg., Peoria 2.
Secretary: Harry H. Boyle, 2376 E. 71st St., Chicago 49.

Indiana State Pediatric Society

President: Dr. Harold D. Lynch, Evansville.
Secretary: Dr. L. T. Meiks, Indianapolis.

Iowa Pediatric Society

President: Dr. John McKitterick, 315 Tama Bldg., Burlington.
Secretary: Dr. James Dunn, 501 Davenport Bank Bldg., Davenport.

Massachusetts Hospital Association

President: Dr. Philip D. Bonnet, Administrator, Massachusetts Memorial Hospitals, Boston.
Executive Secretary: Henry G. Brickman, 14 Somerset St., Boston 8.
Place: Boston. Time: Annual Meeting, January, 1953.

Michigan State Medical Society, Pediatric Section

President: Dr. Horace L. French, 301 Seymour Ave., Lansing.
Secretary: Dr. Park S. Bradshaw, 1014 Jefferson St., Muskegon.
Place: Detroit: Time: September, 1952.

Montana Pediatric Society

President: Dr. Orville M. Moore, 555 Fuller Ave., Helena.
Secretary: Dr. Joseph W. Brinkley, 410 Central Ave., Great Falls.
Place: Variable. Time: Spring and fall.

Nebraska Pediatric Society

President: Dr. George J. Klok.
Secretary-Treasurer: Dr. Donald C. Nilsson, 115 N. 40th St., Omaha.
Place: Children's Memorial Hospital. Time: 6 p.m., dinner, third Thursday of each month from October to June, inclusive.

New Hampshire Pediatric Society

President: Dr. Douglass W. Walker, Laconia.
Secretary: Dr. Wm. D. Penhale, Concord.
Place. Alternately Concord, Hanover, Laconia, and Manchester. Time: Four times a year.

New Mexico Pediatrics Society

President: Dr. M. K. Wylder, Suite 14, Medical Arts Sq., Albuquerque.
Secretary: Dr. Ly Werner, Suite 25, Medical Arts Sq., Albuquerque.
Place: Variable. Time: Every two or three months.

North Carolina Pediatric Society

President: Dr. J. A. Shaw, 107 Bradford Ave., Fayettesville.
Secretary: Dr. Bailey Webb, 809 W. Chapel Hill St., Durham.
Place: Pinehurst. Time: May 6, 1952.

South Carolina Pediatric Society

President: Dr. Walter Moore Hart, 117 W. Cheves St., Florence.
Secretary: Dr. John R. Paul Jr., 82 Rutledge Ave., Charleston.
Place: Columbia, S. C. Time: Second Monday and Tuesday in September; Sept. 8 and 9, 1952.

Tennessee Pediatric Society

President: Dr. O. L. Von Canon, 846 McCallie Ave., Chattanooga.
Secretary: Dr. Oliver W. Hill, 4807 Newcom Ave., Knoxville.

Texas Pediatric Society

President: Dr. C. S. E. Touzel, 1111 Pennsylvania Ave., Fort Worth.
Secretary: Dr. M. C. Carlisle, 1410 Austin Ave., Waco.
Treasurer: Dr. Edith Bonnet, 228 Medical Arts Bldg., San Antonio.
Place: Dallas. Time: Oct. 17 and 18, 1952.

Virginia Pediatric Society

President: Dr. Edwin L. Kendig Jr.
Secretary: Dr. T. J. Humphries.

Wisconsin State Medical Society

Chairman: Dr. Franklin J. Mellencamp, 1513 E. Capitol Dr., Milwaukee 11.
Secretary: Dr. E. H. Pawsat, 44 S. Marr St., Fond du Lac.

Local

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. C. T. J. Dodge, 15457 Euclid Ave., Cleveland 12.
Secretary: Dr. Beulah Wells, 10515 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p.m., October, December. February, and March.

Baltimore City Medical Society, Pediatric Section

President: Dr. Wilson Grubb, 4 E. 33d St., Baltimore 18.
Secretary: Dr. Gibson J. Wells, 3101 St. Paul St., Baltimore 18.
Place: 1211 Cathedral St., Baltimore 1. Time: 8:30 p.m., second Tuesday in November, January, and March.

Bronx Pediatric Society

President: Dr. M. H. Grand, 1749 Grand Concourse, New York.
Secretary: Dr. Charles T. Fried, 1220 Grand Concourse, New York.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August, and September.

Brooklyn Academy of Pediatrics

President: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn.
Secretary: Dr. Henry Cohen, 1761 E. 19th St., Brooklyn.
Place: Granada Hotel, Brooklyn. Time: 8:45 p.m., fourth Wednesday of February, March, April, October, and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold.
Secretary: Dr. Richard A. Downey.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p.m., first Monday of each month, September to June.

Central New York Pediatric Club

President: Dr. Frank Williams, 58 Swan St. S., Albany.

Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester.

Place: Various cities in New York State; fall meeting jointly with Upper New York State Academy of Pediatrics. Time: Third Tuesday of April and October.

Central Ohio Pediatric Society

President: Dr. E. V. Turner, 2479 E. Main St., Columbus.

Secretary: Dr. James Beasley, Lancaster.

Place: As announced. Time: Third Wednesday of September, November, January, March, and May.

Chicago Pediatric Society

President: Dr. George F. Munns.

Secretary: Dr. Matthew M. Steiner.

Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. Nelson W. Ryan, 1743 Madison Rd., Cincinnati.

Secretary: Dr. Joseph E. Ghoury, 2546 Auburn Ave., Cincinnati.

Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dade County Pediatric Society

President: Dr. Lynn Whelchel, DuPont Bldg., Miami, Fla.

Secretary: Dr. Howard Engle, 311 Lincoln Rd., Miami Beach, Fla.

Dallas Pediatric Society

President: Dr. Floyd A. Norman, 4325 Cole Ave., Dallas.

Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave., Dallas.

Place: Children's Hospital of Texas. Time: 6:30 p.m., first Thursday in each month.

Detroit Pediatric Society

President: Dr. Ruben Meyer, 938 Maccabees Bldg., Detroit.

Secretary: Dr. W. W. Zuelzer, Children's Hospital of Michigan, Detroit.

Place: Variable. Time: Five times a year.

Honolulu County Pediatric Society

President: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu.

Corresponding Secretary and Treasurer: Dr. John H. Peyton, Kauikeolani Children's Hospital, Honolulu.

Honolulu Pediatric Society

President: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu.

Recording Secretary: Dr. M. H. Hasegawa.

Corresponding Secretary: Dr. John Peyton, Kauikeolani Children's Hospital, Honolulu.

Place: At doctors' homes in rotation. Time: 6 p.m., third Thursday of each month.

Houston Pediatric Society

President: Dr. Emanuel B. Brandes, 3101 Fannin St., Houston.

Secretary: Dr. Robert D. Lomas, 5101 Fannin St., Houston.

Place: River Oaks Country Club. Time: 7:30 p.m., fourth Tuesday of each month.

Kansas City Southwest Pediatric Society

President: Dr. Frank Hogue, Plaza Medical Bldg., Kansas City, Mo.

Secretary: Dr. S. J. Kranson, Truman Rd. and Ash, Independence, Mo.

Place: University Club, Kansas City, Mo. Time: On call.

Long Beach Pediatric Society

President: Dr. Kenneth Berkaw, 211 Cherry Ave., Long Beach, Calif.

Secretary: Dr. C. W. Latshaw, 3821 Atlantic Ave., Long Beach, Calif.

Place: Victor Hugo Restaurant, 730 E. Broadway. Time: First Tuesday night of every month.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Sidney Rosin, 6230 Wilshire Blvd., Los Angeles.

Secretary: Dr. Arthur J. Holmes, 65 N. Madison Ave., Pasadena 1.

Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd., Los Angeles. Time: Second Thursday of alternate months beginning in September.

Medical Society of the County of Kings and Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Irving S. Pearlman, 7602 Bay Pkwy., Brooklyn.

Secretary: Dr. Irving Weinstock, 350 Ocean Ave., Brooklyn.

Place: Kings County Medical Society Bldg., 1313 Bedford Ave., Brooklyn. Time: 8:45 p.m., fourth Monday of April, October, November, January, and March.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington 20.

Secretary: Dr. John E. Cassidy, 5402 Connecticut Ave. N.W., Washington.

Place: Medical Society Bldg., 1718 M St. N.W., Washington. Time: Spring and fall.

Memphis Pediatric Society

President: Dr. James G. Hughes, 20 S. Dunlap, Memphis.

Secretary: Dr. George S. Lovejoy, 609 N. Highland, Memphis.

Place: Rotated among four hospitals. Time: 7:30 p.m., second Tuesday of each month.

Milwaukee Pediatric Society

President: Dr. Franklin Mellencamp, 1513 E. Capitol Dr., Milwaukee.

Secretary: Dr. Karl Beck, 1411 Wauwatosa Ave., Milwaukee.

Place: Milwaukee University Club. Time: Second Wednesday of February, April, June, and October.

Mobile Pediatric Society

President: Dr. Daniel Sullivan, 1420 Government St., Mobile, Ala.

Secretary: Dr. Robert O. Harris III, 1514 Government St., Mobile, Ala.

Place: Admiral Semmes Hotel. Time: 7:30 p.m., fourth Thursday of September, November, January, March, and May.

Nashville Pediatric Society

President: Dr. Thomas Weaver, Bennie Dillon Bldg., Nashville, Tenn.

Secretary: Dr. Ethel Walker, 3415 West End Ave., Nashville, Tenn.

Place: Homes of members. Time: Third Thursday of every month.

Nassau Pediatric Society

President: Dr. Daniel Blitz, 1 Club Drive, Woodmere, N. Y.

Secretary-Treasurer: Dr. David J. Posner, 98 Wolcott Rd., Levittown, N. Y.

Place: Garden City Hotel, Garden City, L. I., N. Y. Time: 7:30 p. m., second Monday of October, December, February, April, and June.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. Jerome L. Kohn, 50 W. 96th St., New York 25.

Secretary: Dr. Lawrence B. Slobody, 1 E. 105th St., New York 12.

Place: New York Academy of Medicine, 2 E. 103d St. Time: 8:30 p.m., second Thursday of each month, November to May, inclusive.

Northern California Pediatric Society

President: Dr. John A. Anderson, Stanford Hospital, 2351 Clay St., San Francisco 15.

Secretary: Dr. Edward Campion, 1018 E St., San Rafael.

Place: San Francisco. Time: Quarterly, as speakers are available.

Oklahoma City Pediatric Society

President: Dr. C. M. Bielstein, 301 N.W. 12th St., Oklahoma City.

Secretary: Dr. Louis Frank, 1200 N. Walker St., Oklahoma City.

Place: Oklahoma Club. Time: On call.

Philadelphia Pediatric Society

President: Dr. Irving J. Wolman, 1740 Bainbridge St., Philadelphia 46.

Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.

Place: College of Physicians, 19 S. 22d St. Time: 8:30 p.m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. Christian John Stoecklein, 519 Medical Arts Bldg., Pittsburgh 13.

Secretary-Treasurer: Dr. James W. Stirling, 694 Lincoln Ave., Pittsburgh 2.

Place: Western State Psychiatric Institute and Clinic. Time: Second Friday in October, December, February, and April.

Queens Pediatric Society

President: Dr. Samuel Dillon, 119-20 Rockaway Beach Blvd., Rockaway Park, N. Y.

Secretary: Dr. Moe Goldstein, 111-32 76th Ave., Forest Hills, N. Y.

Place: Seminole Club, 112th St. and 70th Rd., Forest Hills, N. Y. Time: Second Tuesday in October, December, February, and April.

Richmond Pediatric Society

President: Dr. Hobart T. Dougan, 1832 Monument Ave., Richmond 20, Va.

Secretary: Dr. Robert A. Hoffman, 1001 W. Franklin St., Richmond 20, Va.

Place: Medical College Hospital. Time: 8 p.m., third Thursday of each month, except June, July, and August.

San Antonio Pediatric Society

President: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.

Secretary: Dr. Virginia S. Stovall, 1116 S. Texas Bldg., San Antonio 5.

Time: 7:30 p. m., supper, first Tuesday of each month.

Seattle Pediatric Society

President: Dr. Norman Cline.

Secretary: Dr. John Sterner.

Place: College Club. Time: 6:30 p.m., fourth Friday of each month from September to June.

St. Louis Pediatric Society

President: Dr. Maurice J. Lonsway.

Secretary: Dr. John C. Herweg.

Place: Candlelight House, 7800 Clayton Rd. Time: 6:30 p.m., second Thursday of each month from October to May, inclusive.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Fred J. Chapin, 101 John St., Bay City.

Secretary-Treasurer: Dr. George H. Lowrey, University Hospital, Ann Arbor.

Place: University Hospital, Ann Arbor. Time: October, 1952.

Waco Pediatric Society

President: Dr. J. M. Garrett, 1408 Austin Ave., Waco, Texas.

Secretary: Dr. C. G. Shellenberger, 1318 Austin Ave., Waco, Texas.

Place: 1917 Austin Ave., Waco, Texas. Time: Third Tuesday of each month.

Westchester County Medical Society, Pediatric Section

President: Dr. Herbert Kahan, 650 Main St., New Rochelle, N. Y.

Secretary: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.

Place: The Roger Smith Hotel, White Plains, N. Y. Time: Four dinner meetings a year, November, February, April, and June.

Western Michigan Pediatric Society

President: Dr. A. Morgan Hill, 310 Fulton, E., Grand Rapids.

Secretary: Dr. John C. Montgomery, 1810 Wealthy St., S.E., Grand Rapids.

Place: Two meetings in Grand Rapids, two elsewhere. Time: First Wednesday of October, November, April, and May.

Wichita Pediatric Society

President: Dr. Vincent Scott, Schweiter Bldg., Wichita, Kan.

Secretary: Dr. William F. McGuire, 3241 E. Douglas, Wichita, Kan.

Place: Homes of members. Time: 8:30 p.m., first Thursday, October through May.

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**J. Pediat. 39:325, 1951*

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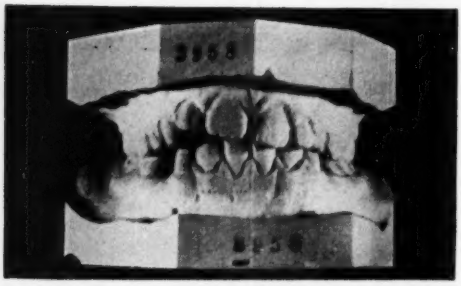

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Meat...

and Its Important Contribution of Essential Amino Acids

Although the daily allowance of protein recommended for human beings has been established for some time,[1] only very recently has a recommended daily intake of individual essential amino acids been proposed.[2] These new criteria now give a more accurate means for nutritionally evaluating the protein contribution of meat than was possible just on the basis of the gross amount of protein meat provides.

The table which follows gives the proportions of the recommended daily intake of individual essential amino acids provided by six ounces of cooked meat, the approximate average per capita daily consumption in the American diet. Note that though furnishing about 52 per cent of the daily protein allowance for a normal adult male, six ounces of meat supplies more than the recommended daily intake for a majority of the essential amino acids and a goodly proportion of the recommended intake of the remainder.

Percentages of Recommended Daily Intake of Eight Essential Amino Acids and of Protein Contributed by 6 Oz. of Cooked Meat*

Essential Amino Acids	Beef[3]	Lamb[4]	Pork[4]
L-Isoleucine	141	121	127
L-Leucine	150	120	125
L-Lysine	202	163	172
L-Methionine	42	34	40
L-Phenylalanine	70	63	70
L-Threonine	160	169	183
L-Tryptophan	90	90	100
L-Valine	136	107	113
Protein	56	49	51

*In the calculations, averages of the percentages of protein in six different cuts of each type of cooked meat were used, as were averages of the percentages of the amino acids in the protein of the respective cuts.

Every kind and cut of meat is not only an excellent source of the essential amino acids but also of the nonessential amino acids, the B group of vitamins, iron, and other essential minerals. Morever, meat is rapidly and almost completely digested, has a stimulating influence upon appetite and digestion, and gives a gratifying sense of satiety. All these nutritional and physiologic advantages of meat fully justify its prominent place in normal diets of persons of all ages and in many special diets.

REFERENCES

1. Recommended Dietary Allowances, National Research Council, Reprint and Circular Series, No. 129, Washington, D. C., 1948.
2. Rose, W. C.: Half-Century of Amino Acid Investigations, Chem. and Eng. News *30*:2385 (June 9) 1952.
3. Greenwood, D. A.; Kraybill, H. R., and Schweigert, B. S.: Amino Acid Composition of Fresh and Cooked Beef Cuts, J. Biol. Chem. *193*:23 (Nov.) 1951.
4. Schweigert, B. S.; Guthneck, B. T.; Kraybill, H. R., and Greenwood, D. A.: The Amino Acid Composition of Pork and Lamb Cuts, J. Biol. Chem. *180*:1077 (Oct.) 1949.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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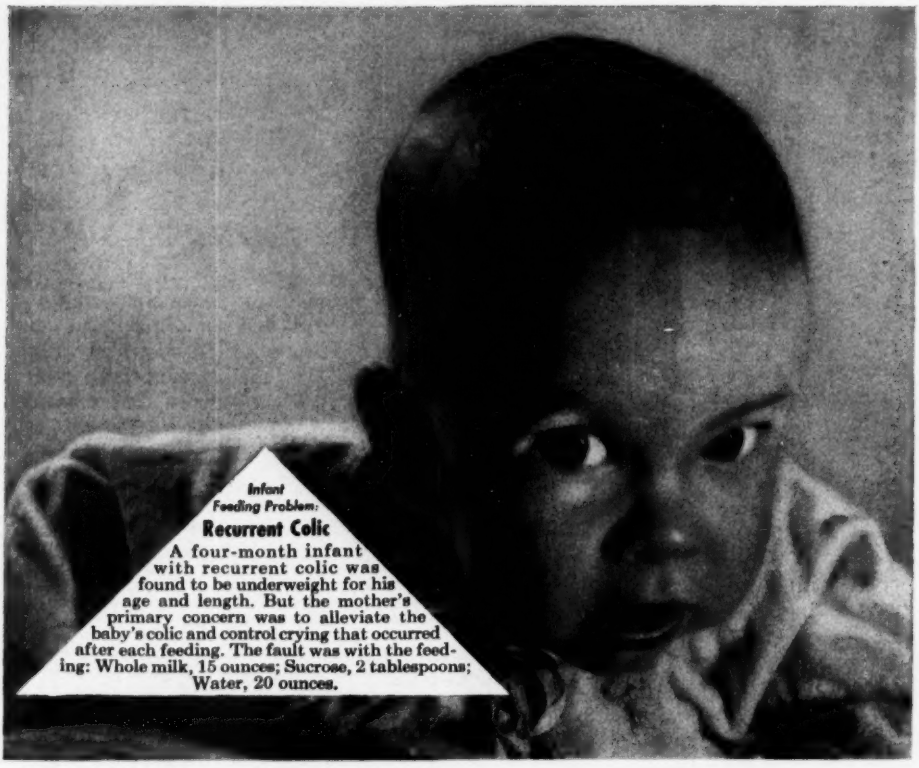
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Feeding Problem:
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A four-month infant with recurrent colic was found to be underweight for his age and length. But the mother's primary concern was to alleviate the baby's colic and control crying that occurred after each feeding. The fault was with the feeding: Whole milk, 15 ounces; Sucrose, 2 tablespoons; Water, 20 ounces.

Recommendation: The formula was concentrated to fulfill the total caloric requirement per pound body weight. Hunger was the cause of crying. And failure to eructate the swallowed air produced intestinal pain. Further crying resulted in swallowing more air. The vicious cycle was broken by gradual concentration into the following formula:

Whole milk, 25 ozs.
Karo Syrup, 3 tablespoons
Water, 10 ozs.
} **7 ozs. q 4 h x 5 feedings**

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. . . prescribed for 3 generations

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2. Karo® Syrup is sterilized . . . bacteria-free, safe for feeding prematures, newborns, other infants and children.
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4. Red Label and Blue Label Karo are interchangeable in all formulas. A tablespoon of Karo Syrup yields 60 calories.

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Bibliography:

1. Frank, P.F., Wilcox, C., and Finland, M.: In Vitro Sensitivity of Coliform Bacilli to Seven Antibiotics, J. Lab. & Clin. Med. *35*:188 and 205, 1950.
2. Jawetz, E. and Coleman, V.R.: Laboratory and Clinical Observations on Aerosporin (Polymyxin B), J. Lab. & Clin. Med. *34*:751, 1949.
3. Pulaski, E.J. and Rosenberg, M.L.: Use of Polymyxin in Gram Negative Urinary Tract Infections, J. Urol. *62*:564, 1949.
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5. Lieberman, D. and Jawetz, E.: Treatment of Chronic Shigella Infections in Children with Oral Polymyxins. Pediatrics *18*:249, 1951.
6. Jawetz, E.: Infections with Pseudomonas aeruginosa Treated with Polymyxin B, Arch. Int. Med. *89*:90, 1952.

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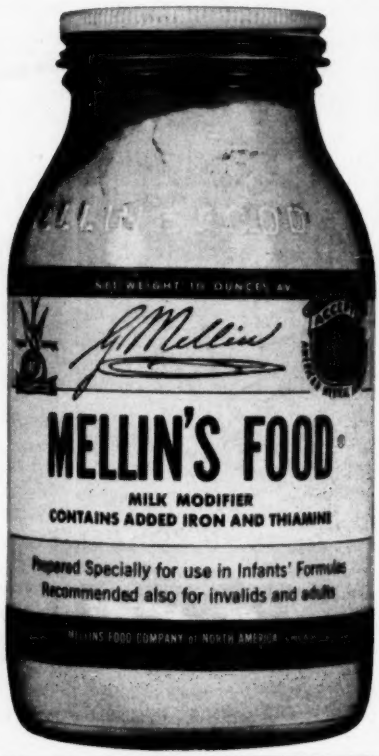
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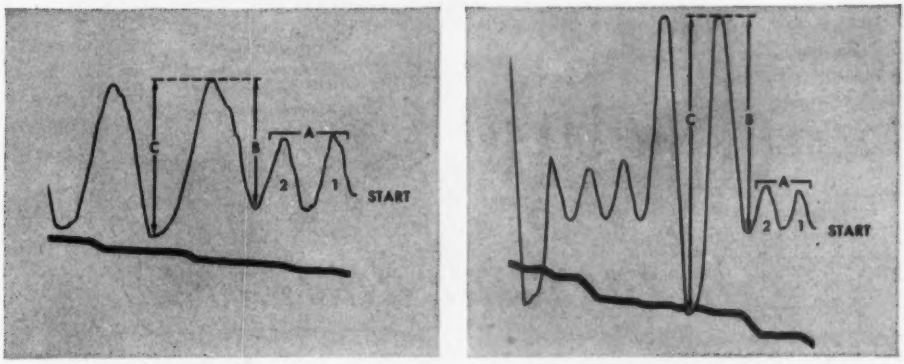

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Schwartz, E., *J.A.M.A.* 147: 1734–1737. Dec. 29, 1951.

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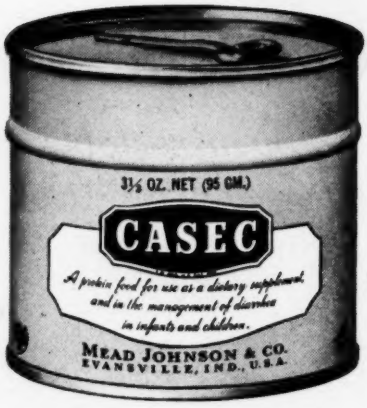
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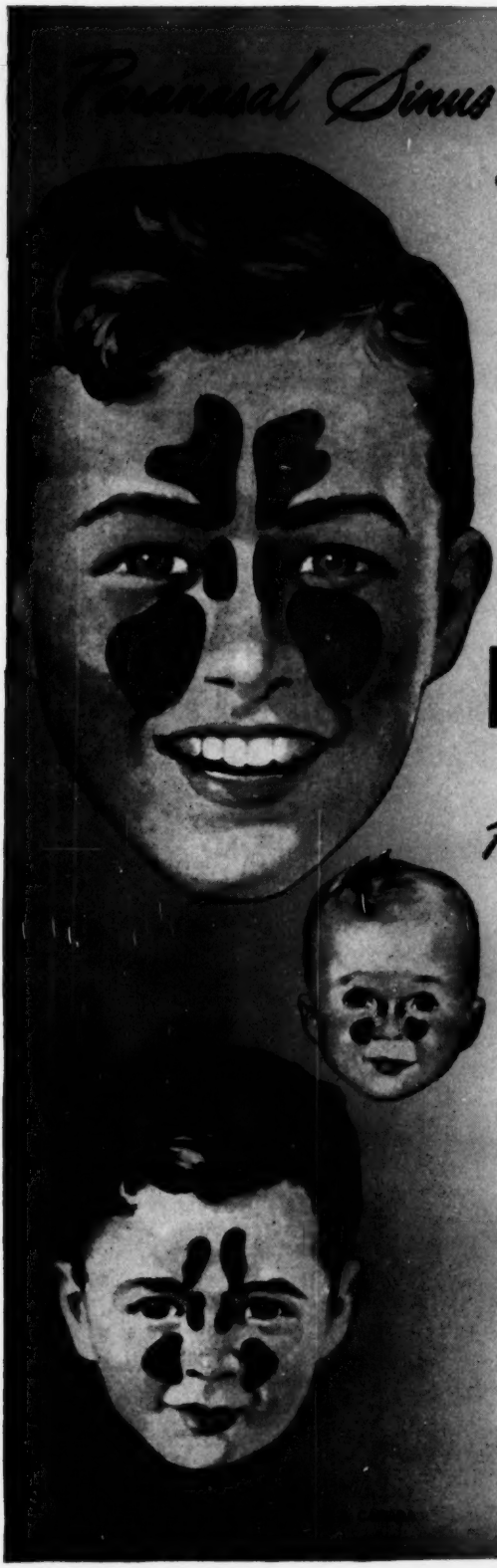

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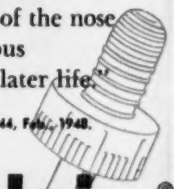
— Burgess, T. S.: Jour. Med. Assn. Georgia, 37:44, Feb., 1948.



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